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GLYCOGEN STORAGE DISEASE

OBSERVATIONS ON THE PATHOLOGIC PHYSIOLOGY OF TWO CASES OF THE HEPATIC FORM OF THE DISEASE

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GLYCOGEN storage disease, first described by von Gierke in 1929,[2] is an uncommon condition of childhood, and opportunities for studying the pathologic physiology are rare. Van Creveld summarized the experiences with the disease in 1939[3] but was unable to formulate a clear picture of the background of the disturbance; further information was needed in many directions. We have had the opportunity to observe two typical cases of the disease and to add certain facts to the accumulated knowledge. The present report concerns these investigations and the conclusions reached regarding the nature of the condition.

A clinical diagnosis of glycogen storage disease, or as it is commonly called, glycogen disease, cannot always be made with precision for the criteria necessary to establish the diagnosis are not clearly defined. The variations in symptoms and findings described in the available case reports lead one to suspect that more than one disease entity may be included under the name of glycogen disease. In order to minimize the confusion which results from our present lack of knowledge, it would seem desirable to direct attention first toward certain well-defined groups within the whole. Unless this is done, new data run a risk of becoming a meaningless average of two or more dissimilar conditions.

The two cases presented in this report belong to the so-called hepatic form of the disease. We believe that this form constitutes a clinical and physiological entity, and that *all* of the following criteria should be satisfied before listing a case in this category:

1. Marked enlargement of the liver
2. Rapid development of hypoglycemia and ketosis when food is withheld
3. A subnormal or absent response of the blood sugar to an injection of epinephrine

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One of the cases was referred through the courtesy of Dr. Paul Hogg of Norfolk, Virginia, and the other by Dr. J. Buren Sidbury of Wilmington, N. C. The latter case was reported by Drs. Hogg and Sidbury in 1937.[1] Part of the technical work was carried out by Mrs. Charlotte Kajdi. The metabolism chamber used for the respiratory quotient studies was made available by a grant from the Rockefeller Foundation Fluid Research Fund of the School of Medicine of the Johns Hopkins University.

4. Chemical analysis showing a glycogen content in the liver of 12-16 per cent of the wet weight, and no marked increase in fat
5. Abnormal stability of the liver glycogen after death or in vitro

Additional studies may add support to the diagnosis but do not appear to be in any way specific or consistent. Other conditions may give one or more of the criteria, but without the whole, no confidence can be placed on the diagnosis. The importance of making an exact diagnosis should be emphasized, for as will be mentioned later, the goal of treatment in true glycogen storage disease differs from that in other conditions which may simulate the symptoms. The technique necessary to establish the criteria is not difficult and can be carried out in the laboratory of any well-equipped hospital.

CLINICAL OBSERVATIONS

CASE 1.—The patient was a 15-month-old female child. Birth was normal, weight 2.5 kg. Development, feeding habits, and general health were not unusual. Although the abdomen had been considered prominent, it was not until the occurrence of a severe respiratory infection at the age of 1 year that the liver was found to be unusually large and firm. Poor appetite, listlessness, and slow gain in weight persisted for several months after recovery from the infection. There were no complaints referable specifically to the metabolic disturbance. Physical examination was negative except for the enlargement of the liver which extended nearly to the iliac crest. Withdrawal of food for only six hours resulted in hypoglycemia and beginning ketosis. The blood sugar was increased little by a subcutaneous injection of epinephrine. The laboratory data are presented in Table I and Chart 1. Biopsy studies confirmed the diagnosis of glycogen disease.

TABLE I. DATA FROM CHILD WITH HEPATIC FORM OF GLYCOGEN STORAGE DISEASE

Case 1 Female Aged 15 months Weight 8.8 kg. Height 76 cm.

			BLOOD SUGAR MG. PER 100 C.C.						
TEST	DATE	DOSE	FAST	15 MIN.	30	60	90	120	180
Epinephrine tolerance test	9/18/40	0.2 mg. subcutaneously	46	50	54	90	93	--	--
Dextrose tolerance test	9/27/40	3 Gm. per kg. orally	49	--	92	120	--	134	130
Dextrose insulin test	9/23/40	Dextrose 3 Gm. per kg., insulin ¼ U. per kg. subcutaneously	62	--	108	108	--	98	133

Blood glycogen	48	mg. per 100 c.c.
Blood cholesterol	198	mg. per 100 c.c.
Liver fat	4	Gm. per 100 c.c.
Liver glycogen (biopsy)	15	Gm. per 100 c.c.
Liver glycogen after standing at 26° C. for 28 hours	15.8	Gm. per 100 c.c.
Liver glycogen mixed with "normal" human liver for 28 hours	11	Gm. per 100 c.c.
Muscle glycogen	0.95	Gm. per 100 c.c.
Basal metabolism	440	Cal. per 24 hours

CASE 2.—The patient was admitted to the Johns Hopkins Hospital for study at the age of 5¼ years. The diagnosis in this boy had been made at the age of 16 months by Drs. Hogg and Sidbury, who reported the case at the time.[1] Birth had been normal, weight 3.9 kg. Infancy also had been uneventful except for several attacks of diarrhea and vomiting, a single episode of otitis media, and an eczema which was attributed to mild egg sensitivity. Physical and mental development had appeared normal although at the age of 16 months he had not yet learned to walk. The mother had noticed that the abdomen seemed prominent at the age of 2 months and thereafter the enlargement had been slowly progressive. Physical examination at this time showed a generally flabby musculature, and an enlarged firm liver which extended to the iliac crest on the right and to the umbilicus on the left. Fasting

blood sugar values varied from 66 to 93 mg. per 100 c.c. of blood. Acetone was consistently present in the urine in amounts varying from 1 to 3 plus. A subcutaneous injection of epinephrine caused almost no rise in the blood sugar. The blood lipids were found to be abnormally high.

At the age of 18 months, he had an episode of semiconsciousness at 7:30 A.M. which lasted about two hours but was not associated with convulsions. Following tonsillectomy at the age of 3 years, he bled so profusely that emergency transfusions were necessary. One month later, at the onset of pneumonia he had mild jaundice lasting a week. Since then the only complaint has been dyspnea with mild exertion. General health has remained good. Growth in height has been somewhat retarded although weight has never been below normal. At the Johns Hopkins Hospital the diagnosis of glycogen storage disease was confirmed by biopsy and by the chemical and metabolic studies which we are reporting. The general laboratory data are presented in Table II.

TABLE II. DATA FROM CHILD WITH HEPATIC FORM OF GLYCOGEN STORAGE DISEASE

Case 2 Male Aged 5½ years Weight 22 kg. Height 102 cm.

TEST	DATE	DOSE	BLOOD SUGAR MG. PER 100 C.C. FAST	30 MIN.	60	120	180
Epinephrine tolerance test	10/20/36*	0.4 mg. subcutaneously	66	68	71	69	68
Dextrose tolerance test	1/14/41	1.75 Gm. per kg. orally	55	163	119	156	100
Dextrose-insulin test	1/20/41	Dextrose 1.75 Gm. per kg., insulin ⅛ U. per kg. subcutaneously	63	121	114	123	119
Levulose tolerance test	1/ 9/41	1.0 Gm. per kg. orally	99	145	156	122	131

Blood cholesterol	224 mg. per 100 c.c.
Blood glycogen (average of 7)	85 mg. per 100 c.c.
Serum proteins	5.4 Gm. per 100 c.c.
Serum phosphatase	17.3 Bodansky units
Clotting time	13-19 minutes
Prothrombin activity (Quick)	76 per cent
Prothrombin activity after Vitamin K	100 per cent
Liver glycogen	
(a) biopsy	13.9 Gm. per 100 c.c.
(b) after standing at 26° for 28 hr.	12.4 Gm. per 100 c.c.
(c) mixed with rabbit liver for 28 hr.	3.0 Gm. per 100 c.c.
(d) incubated at 37° for 3 hours with	6.0 Gm. per 100 c.c.
pancreatic amylase	
phosphorylase (liver)	10.4 Gm. per 100 c.c.
Campolon liver extract	13.6 Gm. per 100 c.c.
Fuqua's liver extract	13.5 Gm. per 100 c.c.
Muscle glycogen	4.7 Gm. per 100 c.c.
Basal metabolism	860 Cal. per 24 hours

*Reported by Hogg and Sidbury.[1]

The two cases presented a strikingly similar clinical picture. In addition, the microscopic appearance of the sections obtained at biopsy were indistinguishable from each other or from pictures published in other reports. Both showed a very high level of liver glycogen which on standing was found to be abnormally stable. The fat content of the liver in both cases was normal. Since the two cases offered an unusual opportunity for studying the pathologic physiology of glycogen storage disease, an attempt was made to investigate the nature of the enzymatic deficiency in the liver. In addition, studies of the disturbed carbohydrate metabolism were carried out and various measures instituted in attempts to correct the abnormalities found. Changes in blood lipids, blood glycogen, nitrogen equilibrium, and urinary pentose excretion were also observed.

METHODS

The procedures employed were standard ones, most of which have been in use in this clinic for several years. For the determination of glycogen, approximately 0.5 gram of tissue (liver or rectus muscle) obtained at operation was freed from blood by blotting with filter paper and immediately placed in a weighed and stoppered pyrex test tube containing 2 c.c. of 30 per cent potas-

sium hydroxide. As soon as possible this was warmed gently over an open flame until digestion began to take place. When cool, the tube was reweighed to determine the size of the sample. In the case of the liver, one portion (A) was added to a tube of 30 per cent potassium hydroxide whereas the second portion (B) was placed in a dry, weighed, and stoppered test tube and after reweighing, was allowed to stand at room temperature (23 to 26° C.) for twenty-four hours before adding the potassium hydroxide. Thereafter the analysis followed the technique of Good, Kramer, and Somogyi,[4] the final determination of glucose being made by the Hagedorn-Jensen method.[5] A third sample (C) was ground with sand, mixed with normal liver of known weight and glycogen content and treated as B.

At the time of biopsy, which was done under procaine and light ether anesthesia, observations were made on the gross pathology of the liver, and pieces were removed for microscopic and chemical studies and for tissue respiration experiments in a Warburg apparatus.

The chemical studies were carried out with freshly cut liver slices which were first blotted with filter paper to absorb all possible blood and then weighed on a torsion balance. They were then introduced into tubes containing various enzyme preparations with which they were incubated at 37° C. for three hours. At the end of this period potassium hydroxide was added and the glycogen measured by the usual procedure. Suitable controls were carried out. The enzyme preparations studied were:

a. A sample of *muscle phosphorylase* supplied by Dr. Carl F. Cori
b. *Liver phosphorylase* prepared from rabbit liver by the method of Cori, Cori, and Schmidt,[6] used with an activator mixture providing a final dilution of 0.005 M magnesium sulfate and 0.001 M adenylic acid in M/30 phosphate buffer, pH 7.2
c. A sample of concentrated *pancreatic amylase* supplied by the Takamine Laboratories, Inc.
d. A commercial whole liver extract (Campolon) manufactured by the Winthrop Chemical Company
e. A whole liver extract prepared by Mr. Robert Fuqua in the pharmacy of the Johns Hopkins Hospital, known to be rich in antipernicious anemia factor

Blood glycogen was determined by the van Creveld method.[7] In order to obtain enough blood glycogen to carry out identifying tests, the material obtained from several large samples of blood was pooled and reprecipitated three times. This was dissolved in water to make a 1 per cent solution, and a similar concentration of rabbit liver glycogen used for a control. The iodine test for glycogen was made by determining the smallest concentration of both solutions which would give a recognizable color when 1 drop of 25 per cent sodium chloride and 1 drop of tincture of iodine were added to 1 c.c. of the glycogen solution. To test the effectiveness of amylase on the two preparations, a comparison was made of the amount of enzyme solution required to destroy a standard amount of the glycogen as indicated by failure of the iodine test to give the characteristic color. The samples were incubated for thirty minutes at 37° C. Liver fat was determined by the micro method of Josephs.[8] Since some of the details have not yet been published, they are given in the footnote.* Blood lipids were determined by the technique of Holt, Tidwell, and Scott.[9]

*A weighed sample of liver (0.1—0.3 gram) is ground with sand in a small mortar with 5 c.c. of Bloor's Mixture (3 parts of 95 per cent alcohol, 1 part of ethyl ether) and transferred to a 50 c.c. Erlenmeyer flask, washing with two 5 c.c. portions of Bloor's Mixture.

(Footnote cont'd on next page.)

Respiratory quotient and basal metabolism studies were made in an open circuit chamber. The air was collected in a 100 liter gasometer and samples analyzed in the Carpenter-Haldane apparatus. The children were quiet but not necessarily asleep during the respiration periods. Nitrogen analyses by the macro Kjeldahl method were used on urine, stools, and sample diets to determine nitrogen balance.

BIOPSY STUDIES

The gross appearance and consistency of the liver were similar in both of our patients. The color was a light yellowish brown with occasional small areas of bluish red suggesting irregular vascularity. When cut, the liver felt tough and inelastic but not particularly fibrous. This was strikingly different from the light brown friable liver seen in normal animals with a similarly high content of glycogen. Relatively little blood oozed from the cut surfaces.

Fig. 1.—Section of liver obtained at biopsy from a child aged 5½ years with the hepatic form of glycogen storage disease.

Microscopically the specimens of liver showed the typical characteristics described in glycogen storage disease. The cells were greatly enlarged and gave the "plant-like" appearance described by others. By means of Best's carmine stain the cells were shown to contain large amounts of glycogen. Unlike the picture encountered in fatty livers, the nucleus usually remained in a central position, being only rarely shifted to the periphery of the cell. The cytoplasm appeared small in amount and filled with numerous granules which took the

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The flask is heated in a water bath for about ten minutes making up for evaporation by adding more Bloor's Mixture. After standing from 1 to 2 hours, the solution is filtered with suction into a 250 c.c. filter flask and the precipitate washed twice with from 5 to 10 c.c. portions of Bloor's Mixture. The flask containing the filtrate and washings is then placed in a hot water bath and the filtrate evaporated under a partial vacuum with a sufficient current of air to prevent boiling and spattering. When dry and still hot, the sides of the flask are washed down with petroleum ether in four or five successive portions of 1 c.c. each. As soon as the flask has cooled enough to allow the collection of a small amount of petroleum ether at the bottom, this is transferred to a test tube of from 8 to 10 c.c. capacity. The flask is again washed with several 1 c.c. portions of petroleum ether which are added to that in the test tube. The tube and contents are centrifuged to throw down in a coherent mass any precipitate that might be present. The supernatant petroleum ether is then transferred as quantitatively as possible without stirring up the precipitate to a clean, dry, and accurately weighed test tube (75 by 11 mm., thin glass). This is placed in a beaker of water warmed to from 45 to 50° C. and the petroleum ether evaporated off in a current of dry air. When thoroughly dry, the tube with the fat is reweighed to 0.1 mg.

glycogen stain. Fig. 1 shows the appearance of a typical section from Case 1 and is indistinguishable from Case 2.

The section of muscle obtained from Case 1 showed normal structure without evidence of excessive glycogen, a fact which was confirmed by chemical analysis. No sections were obtained from the muscle in Case 2 in which the glycogen level was greatly increased.

In order to study the metabolism of the liver cells, two samples from Case 2 were placed in the Warburg apparatus and the oxygen consumption compared to that of normal liver.* The glycogen disease specimens showed a very low metabolic rate per unit of weight, consuming only 12 and 18 per cent as much oxygen in two hours as average normal rat liver. The higher figure, 18 per cent, was obtained in a medium containing added glucose. In searching for an explanation of these differences, it became evident that per unit of weight, the liver in glycogen storage disease contained fewer active cells and more inert glycogen than the normal. Measurements were therefore made of the average diameter of the liver cells in glycogen storage disease and in normals and the relative volume of the cells calculated. Figures thus obtained indicated that the cells in glycogen storage disease are from eight to ten times the size of normal cells. In other words, a unit weight of liver from glycogen storage disease contains only from 10 to 12 per cent as many cells as the normal, and on this basis the data on oxygen consumption would fall within the normal range. Attempts were made to grow the liver cells by a tissue culture technique which has proved satisfactory for normal liver. However, only fibroblasts developed.†

Chemical analysis of the liver specimens confirmed the diagnosis of glycogen storage disease. As will be seen in Tables I and II, the glycogen content of the liver in both cases was approximately 15 per cent, which is probably a maximal figure for the human liver. When allowed to stand in a test tube for twenty-eight hours at 25 to 26° C. the glycogen content of both specimens showed almost no decrease. Under similar circumstances normal liver would lose from 75 to 100 per cent of its glycogen.[10] When mixed with normal rabbit liver, the glycogen in Case 2 was rapidly broken down. In Case 1, the change was less marked. However, the "normal" liver used in the latter was obtained from an adult patient dying from a chronic wasting disease and may not have been comparable to fresh rabbit liver. The concentration of fat in the liver of both cases was found to be in the low normal range. The chemical findings, therefore, confirm the pathologic picture in establishing a clear diagnosis of glycogen storage disease.

The fact that normal liver contains a substance which is lacking in the liver of glycogen storage disease, as we have demonstrated as well as by experiments described in the literature, opens the way for the identification of the substance responsible for the deficiency. We have attempted to explore a few of the possibilities by incubating slices of liver from Case 2 with a variety of liver extracts and enzyme preparations. From the results of these experiments, which are presented in Table II, it is quite apparent that liver extracts prepared for the treatment of pernicious anemia exerted no effect on the liver glycogen of this patient. Very little breakdown of glycogen was caused by the muscle phosphorylase, and the performance of the liver phosphorylase under the conditions of the experiment was only a little better. The preparation of pancreatic amylase gave by far the best results, causing a reduction from 13.6 per cent to 6 per cent in the three-hour period.

*Dr. Chalmers Gemmill carried out the studies on the respiration of the liver cells.
†The tissue culture work was done by Dr. George Gey.

At first sight, these observations might suggest that the liver in glycogen storage disease was lacking in the enzyme amylase. Such a conclusion, however, does not seem warranted for several reasons. Since amylase is known to have a powerful glycogen splitting action in slices of normal liver,[11] the observations could be interpreted as evidence of the normal reactivity of the glycogen. Although not related directly to the amylase content of the liver cells, it was nevertheless of interest to find that both blood and urine of this patient contained normal amounts of amylase. In addition, the oral administration of large amounts of the enzyme had no effect on the tendency toward hypoglycemia.

Samples of muscle were obtained from the abdominal wall of both patients at the time of operation. The younger child with less advanced symptoms showed a normal glycogen content of 0.95 per cent, whereas the older child with more widespread symptoms gave an extremely high value of 4.7 per cent.

OBSERVATIONS ON BLOOD GLYCOGEN

The occurrence of an increase in the level of glycogen in the blood of patients with glycogen storage disease has been reported by numerous observers.[12] The amount present, however, has been so small that doubts have sometimes been raised over the assumption that the substance measured was, in reality, glycogen. Furthermore, it is difficult to conceive of a substance with the colloidal properties of glycogen having a natural function in the blood comparable, for example, to its breakdown product glucose. Studies were therefore carried out to investigate the nature and function of the blood "glycogen." As will be seen in Table III, ten normal children and adults gave blood glycogen values

TABLE III. STUDIES OF BLOOD GLYCOGEN FROM CHILD WITH HEPATIC FORM OF GLYCOGEN STORAGE DISEASE

BLOOD GLYCOGEN		
Normal values,	whole blood (5-22)	13.5 mg. per 100 c.c.
Case 1	whole blood	48 mg. per 100 c.c.
Case 2	whole blood	85 mg. per 100 c.c.
Case 2	whole blood incubated with amylase 2 hr. at 37° C.	no change
Case 2	cells	194 mg. per 100 c.c.
Case 2	plasma	5 mg. per 100 c.c.

GLYCOGEN REPRECIPITATED FROM WHOLE BLOOD	
Iodine color reaction	positive
Amylase action	normal
Reduction after hydrolysis	normal
Fermentation after hydrolysis	normal

averaging 13.5 mg. per cent with variations from 5 to 22. The younger patient (Case 1) whose symptoms were milder showed 48 mg. per cent, while the child with the more advanced symptoms (Case 2) had blood glycogen values ranging from 78 to 90 mg. per cent, averaging 85 mg. From the latter patient 60 c.c. of pooled blood were obtained for study.

In order to identify the substance in the blood as glycogen, it was first necessary to get rid of impurities. This was done by dissolving and reprecipitating the material three times. A substance was thus obtained which was sticky in consistency, dissolved readily in water, and in color was somewhat more dirty gray than the control glycogen which had been reprecipitated from rabbit liver. Both were dissolved in water to form a 1 per cent solution. The reactions of the two samples to standard tests for glycogen were indistinguishable except that those from the blood were somewhat less intense. This would suggest that im-

purities were still present. (a) The iodine tests gave the typical wine-red color. (b) The rate of destruction by amylase as measured by the disappearance of the iodine test was essentially the same in both. (c) After hydrolysis with 0.6 N hydrochloric acid, the amount of reducing substance formed was slightly less than the control. (d) The reducing substance of both samples disappeared after fermentation with washed yeast. (e) Bial's test and the phloroglucin test for pentoses gave no reaction with the hydrolysate. Thus it seems clear that true glycogen was present in the blood in appreciable quantities, and that the small variations from the control were quantitative and not qualitative. The significant facts are summarized in Table III.

In order to understand the function of the glycogen in the blood, it seemed necessary to know whether it was present in the serum as a solute, or in the cells as a stored substance. Analysis of the cells and serum separately showed that less than 3 per cent of the total was in the serum, and 97 per cent was in the cells. Attempts to separate the white cells from the red cells were unsuccessful. However, calculations based on the white blood cell counts of 8,000 to 13,000 in this patient, and the fact that the leucocytes constitute from 0.7 to 1.3 per cent of the blood at this level[13] showed that all the glycogen in the blood of this patient could be accounted for by a concentration of from 6 to 10 per cent of glycogen in the leucocytes with none in the erythrocytes. This is in the general order of magnitude found in other tissues in glycogen storage disease, and in the present case compares with the figure of 4.7 per cent in muscle and 13.9 per cent in liver. It seems likely, therefore, as van Creveld has suggested[12a] that the glycogen present in the blood is stored as such in the living leucocytes. Our observations also confirm those of van Creveld in showing that blood glycogen is relatively stable when allowed to stand at room temperature or at 37° C. for from twenty-four to forty-eight hours. However, this does not necessarily indicate an abnormality such as that demonstrated in the liver. It may mean simply that glycogen in the white blood cells like glycogen in the muscles is normally quite stable. Or it could mean that the leucocytes continue to live and maintain their glycogen stores for many hours after removal from the body. At any rate, the function of the glycogen in the blood would be the function of glycogen in the white cells.

In the light of these results, it seems probable that the increased level of blood glycogen represents, in reality, an increase in one of the tissues of the body, namely, the leucocytes. And if as these two cases suggest, high levels correspond to a more widespread involvement of the storage difficulty, a knowledge of blood glycogen levels might be expected to give information concerning the stage of advancement of the disease. Whether or not a high level in the leucocytes affects resistance to infection in these patients cannot be judged at the present time.

OBSERVATIONS ON FAT METABOLISM

During the course of the disease in Case 2, observations were made on the blood lipids. As will be seen from Table IV, all values were distinctly above normal at the age of 2 but at 5½ years the total cholesterol and lipid phosphorus had returned to the upper limit of the normal range, while the total blood lipids and neutral fat were only slightly increased. At the time of the biopsy, liver fat was found to be normal, 3.2 per cent. The significance of these changes in blood lipids is not clear. Since carbohydrate is not readily available for combustion during many hours of the day, it seems probable that fat trans-

TABLE IV. STUDIES OF BLOOD LIPIDS FROM TWO CHILDREN WITH HEPATIC FORM OF GLYCOGEN STORAGE DISEASE

CASE	AGE	TOTAL LIPIDS (GM. %)	NEUTRAL FAT (GM. %)	TOTAL CHOLESTEROL (GM. %)	LIPID PHOSPHORUS (MG. %)
1	15 mo.	1.2			
	16 mo.	2.8			
2	2 yr.	2.8	1.6	0.42	33
	5¼ yr.	1.4	0.8	0.22	15
Normal values		0.5 to 0.7	0 to 0.2	0.1 to 0.23	7 to 14

port and utilization are more active than under normal circumstances. Although our knowledge of the factors entering into these processes is at present too meager to justify conclusions, the observations suggest that lipemia in glycogen storage disease is a phenomenon of early life from which spontaneous recovery may occur.

OBSERVATIONS ON CARBOHYDRATE METABOLISM

It seems probable that the central disturbance in the hepatic form of glycogen storage disease consists in the inability of the liver to supply adequate glucose to the body. Such a deficit in itself would be responsible for certain symptoms of the disease; other symptoms might result from secondary or compensatory mechanisms being brought into action. In the present study, therefore, attempts were made to investigate the changes in carbohydrate metabolism in ways that would help to distinguish the primary from secondary disturbances.

In all cases of glycogen storage disease, including our own, hypoglycemia and ketosis occur together. Ketosis, usually without hypoglycemia, develops in normal children and adults whenever the metabolic needs are supplied predominantly by fat combustion, as in fasting or while consuming a high fat diet. Although under these circumstances hypoglycemia is not common, it has been observed during eight to twenty-four-hour fasts of small infants,[14] during more prolonged fasting of certain older children and adults,[15] and in the presence of liver disease or hypofunction of the adrenal cortex. The occurrence of hypoglycemia with ketosis in glycogen storage disease is not, therefore, evidence of a specific feature of the disease, but suggests only that the normal reactions to starvation are more easily or more frequently brought out than in normal individuals.

This reaction to fasting is demonstrated in the observations made on Case 1, the child of 15 months. As will be seen from Chart 1 a normal blood sugar concentration and a slightly low level of the respiratory quotient were observed during the four-hour intervals between feedings. If, however, one feeding were omitted, the respiratory quotient fell abruptly to the level of fat and protein combustion and hypoglycemia with ketosis developed. The rapidity of the change is such as to suggest that the usual cushion of glycogen reserves is either lacking or ineffective. The reaction is in sharp contrast to the slow changes observed during fasting in normal well-nourished infants. Here from twelve to twenty-four hours of starvation are usually required to bring out ketosis and even then hypoglycemia is not regularly associated—Chart 2. These observations show that in spite of the high and probably maximal level of glycogen known to be present in the liver, this patient with glycogen storage disease reacted to food deprivation as if she had no reserves of glycogen at all. This is, of course, consistent with the known abnormalities of the glycogen demonstrated by chemical means. The symptom of ketosis, therefore, represents a normal metabolic reaction to a deficiency in utilizable glycogen. The development of

hypoglycemia while not strictly a "normal" reaction, probably represents a lag in adjustment to the rapidly shifting metabolic balance. Whether or not an inability of the liver to form glucose from protein contributes to the hypoglycemic tendency is indeterminate at present. The hypoglycemic convulsions which patients with this disease infrequently have, are, of course, the clinical manifestations of the low blood sugar level.

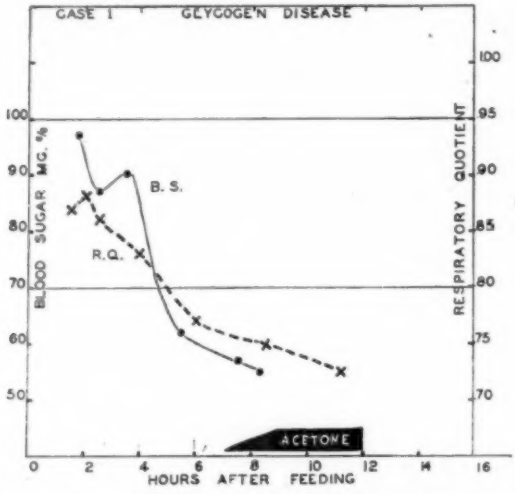

Chart 1.—The rate of fall of the blood sugar and respiratory quotient during fasting in Case 1, a child aged 15 months. The child had been receiving a full feeding previous to the test.

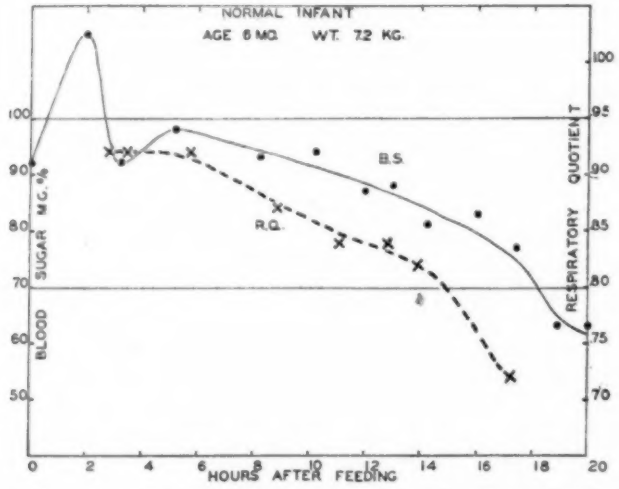

Chart 2.—The rate of fall of the blood sugar and respiratory quotient during fasting in a normal infant aged 6 months whose weight was approximately the same as that of the infant in Case 1 (Chart 1). Note the slow rate of fall of the normal infant in contrast to the infant with glycogen storage disease.

From the clinical history, Case 2 may have gone through a stage similar to this at the corresponding age of from 1 to 2 years, for an episode of semiconsciousness without true convulsions is described. However, when seen at the age of 5½, the changes in carbohydrate metabolism were by no means so simple.

As will be seen in Chart 3, ketosis was present throughout the day although most intense from 4 to 11 A.M. Food reduced the ketosis to a low level during the afternoon, but at night hypoglycemia, ketosis, and a low respiratory quotient developed as in the former case. The reaction to starvation was, therefore, qualitatively similar in both cases.

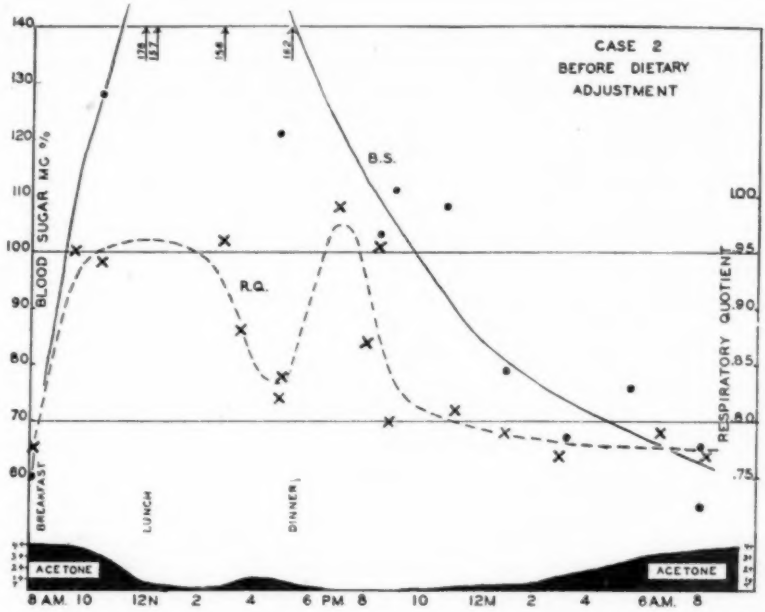

Chart 3.—The variations in blood sugar, respiratory quotient, and acetonuria during the day in a child aged 5½ years with the hepatic form of glycogen storage disease (Case 2).

The variations in blood sugar level throughout the day, observed in this older child, are of interest. As will be seen from Chart 3, following the ingestion of food, the blood sugar rose rapidly from approximately 50 mg. per cent to the abnormally high level of from 140 to 170 mg. per cent and ketosis slowly diminished. Here again, the reaction of the patient with glycogen storage disease has a parallel in the normal individual. It is well known that in prolonged starvation in which ketosis develops comparable in degree to that seen in the early morning in this patient with glycogen storage disease, the ingestion of food or glucose induces a marked and prolonged rise in blood sugar level. This phenomenon is sometimes called "starvation diabetes." It seems probable that this mechanism is operating in the patient with glycogen storage disease to account in part, at least, for the excessive rise in blood sugar level after meals. In addition, the fact that the storehouses for carbohydrate in the body are already filled would interfere with the normal removal of glucose from the blood.

As will be seen also in Chart 3 immediately following breakfast the respiratory quotient rose abruptly to abnormally high levels, somewhat parallel to the rise in blood sugar. Such a high respiratory quotient level is *not* seen in normal individuals under corresponding conditions of starvation and ketosis. Instead, following either a regular meal or glucose, the respiratory quotient rises scarcely at all until the ketosis has disappeared. Usually this delay in response persists for from four to six hours but may continue as long as twenty-

four hours. Furthermore, while a progressive acidosis with blowing off of carbon dioxide may give a falsely high respiratory quotient, this would not appear to be involved in the patient under discussion for the respiratory quotient was highest at the time ketosis and acidosis were diminishing. Observations on the carbon dioxide combining power of the blood also failed to indicate an acidosis. The explanation for the abnormal rise in respiratory quotient probably lies in a rapid conversion of carbohydrate into fat. The liver which is already filled, and probably even saturated with glycogen, can no longer function as a storehouse for ingested carbohydrate. Other tissues are also limited in their ability to deposit glycogen. That portion which cannot immediately be utilized, therefore, is probably shunted into the other energy reservoir by conversion into fat and deposition as such. The conversion of carbohydrate into fat is associated with respiratory quotient levels higher than 1.0. The observed values probably represent a resultant of the respiratory quotient of this conversion combined with the low value of a metabolic mixture derived largely from fat and protein.

The results of the other tests of carbohydrate metabolism are shown in Tables I and II. The injection of epinephrine resulted in a subnormal rise in blood sugar level as would be expected from the known stability of the liver glycogen. The insulin sensitivity test gave a normal response in Case 2, and suggested a mild insulin resistant state in Case 1. The levulose tolerance test resulted in a rise in blood sugar level that was higher and more prolonged than normal and might be interpreted as evidence of liver insufficiency.

OBSERVATIONS ON NITROGEN BALANCE

Since the conversion of protein into glucose is a well-established mechanism compensating for hypoglycemia, it seemed advisable to ascertain the state of the nitrogen balance in glycogen storage disease. Such observations were made in Case 2. After being on a constant average diet for a preliminary period of two days, accurate collections of urine and stool were made over a six-day period. An aliquot portion of the food was collected for analysis. The results of the balance studies showed the patient to be losing an average of 0.3 Gm. of nitrogen a day. Since a normal child of this age should retain from 0.2 to 0.3 Gm. of nitrogen a day,[16] the actual deficit is in the range of from 0.5 to 0.6 Gm. of nitrogen or from 3 to 4 Gm. of protein. Furthermore, administration of methyltestosterone, which has been shown to stimulate nitrogen retention in normal individuals and in certain types of dwarfs,[17] failed to have an effect in this patient. This would also suggest that protein balance was inadequate to permit retention even in the presence of stimulation.

LIVER FUNCTION

Several evidences of liver insufficiency were observed in Case 2. Starvation hypoglycemia is, in itself, an indication that the liver is unable to form adequate glucose from glycogen or from protein. The high and prolonged levulose tolerance test which we have mentioned, and the reduced prothrombin activity of the blood are additional signs of impairment of liver function. It is interesting to note that in spite of this latter insufficiency, the administration of menadione (Vitamin K) induced a quick return of the prothrombin activity to normal. Further evidence of impairment of a hepatic function was shown by the diminished ability to methylate a test dose of nicotinamide given by mouth, an observation made in Case 2 by Dr. Victor A. Najjar and subse-

quently confirmed by him in two other patients with glycogen storage disease. It has been shown by Perlzweig and the Bernheims[18] that such methylation occurs in the liver.

REDUCING SUBSTANCE IN THE URINE

In the course of the routine studies in Case 2 it was found that many specimens of urine contained a reducing substance. This was present chiefly in the more concentrated specimens and reached a proportion of from 0.1 to 0.3 per cent expressed as sugar. It was not fermentable, and gave reactions characteristic of the pentose group. Efforts to determine the exact nature of the substance were unsuccessful.

THERAPY

Attempts to improve the symptoms of the disease and to modify the course met with only slight success. Since amylase was known to have a pronounced action in converting glycogen to glucose, large doses of pancreatic extract were given by mouth and several injections of purified preparations of the enzyme were given intravenously. No appreciable effect on the hypoglycemia was evident. As a means of stimulating protein catabolism to overcome the fasting hypoglycemia, the administration of the blood sugar raising principle of the adrenal cortex was tried. Twenty-five milligrams of compound E (17 hydroxy, 11 dehydrocorticosterone) were given in divided doses in the course of twenty-four hours. The material was given in oil by intramuscular injection. No hyperglycemic effect or influence on nitrogen excretion was noted.

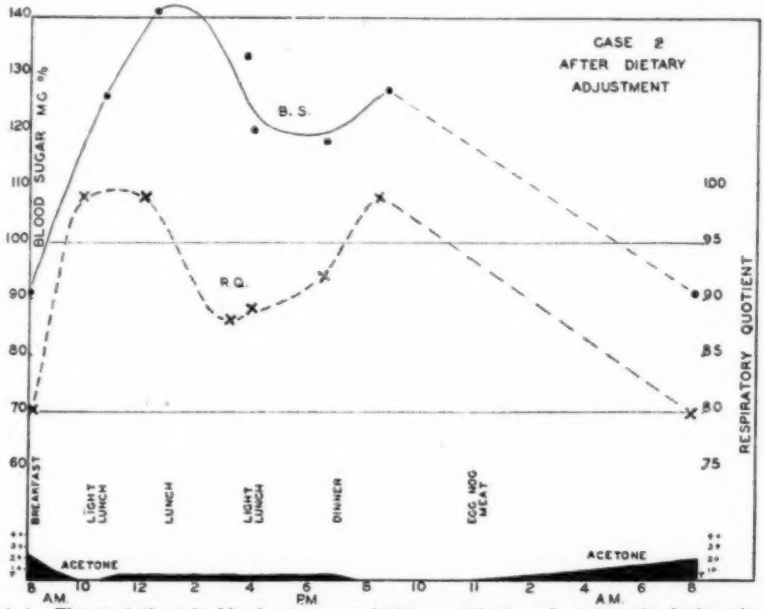

Chart 4.—The variations in blood sugar, respiratory quotient, and acetonuria during the day in Case 2, after improvement in the child's dietary regulation.

We then attempted to stabilize the blood sugar by the device of giving an additional protein meal late at night. This additional protein would, it was thought, serve as an indirect source of carbohydrate, which would tend to prevent the early morning hypoglycemia and ketosis. An evening meal of ground beef and bread was therefore given to the patient between 11 and 11:30 each

night, a welcome addition to his diet. After several weeks of this regime it was found that the hypoglycemia and ketosis in the early morning hours had undergone considerable diminution and the daytime peak in the sugar level had likewise decreased (Chart 4). While on this dietary regime the patient felt better, became more active and the dyspnea disappeared. During the fifteen months since discharge from the hospital he has continued to feel well and has begun to grow at a normal rate. His liver remains as large as ever, however, and ketosis, although less conspicuous than on admission, has not disappeared. It would appear, therefore, that although the fundamental pathologic process may not have been altered, some of its untoward effects have been obviated.

DISCUSSION

Since the original description of glycogen storage disease by von Gierke in 1929, approximately 200 cases have been reported. Some of these have been subjected to careful laboratory tests which have established the diagnosis clearly. Others represent simple clinical observations from which the diagnosis is surmised. Since many of the symptoms of glycogen storage disease can be simulated by other types of disturbances, in particular by excessive accumulations of fat in the liver, it seems important to us that an accurate diagnosis be established in all cases. Not only is this of academic interest, but in addition the therapy recommended for a patient with the hepatic form of glycogen storage disease is different from that needed by an individual whose symptoms result from a disturbance in fat metabolism.

The position of glycogen storage disease as a primary metabolic disease is not well established. The disease appears rather to be a developmental defect involving the enzyme system of specific organs, and usually a single organ—the liver or the heart, rarely the kidney. Evidences of a metabolic disorder are found only in the hepatic cases, so far as our present knowledge goes, and these are attributable directly or indirectly to disturbances in hepatic function. In cases where the heart is involved, the symptoms appear to remain localized.

As discussed previously, most of the symptoms and signs of the hepatic form of the disease can be explained as secondary, tertiary, and quarternary effects of a primary defect in the enzyme system. Fig. 2 presents in diagrammatic form the possible sequence in the development of symptoms. Particular attention should be called to several of these secondary effects of impaired glycogenolysis: (1) hypoglycemia, which may induce cerebral symptoms, stimulate ketosis, and possibly impair resistance to infection; (2) an excessive conversion of carbohydrate into fat leading to obesity; and (3) a negative nitrogen balance caused by the increased formation of sugar from protein in an attempt to sustain the blood sugar level. This negative nitrogen balance may account for the impaired growth often noted in these children.[19]

It is of interest to note that the disturbance in the liver involves more than the glycogenolytic functions. Our own observations revealed a defect in prothrombin formation, a disturbance in methylation, and, in infancy at least, a lipemia which may represent a difficulty in the removal of blood fat by the liver. Other hepatic functions such as the secretion of bile pigment and the formation of plasma proteins do not appear to be affected, although it would be desirable to study these more extensively.

It is our belief that the criteria employed in the diagnosis of hepatic glycogen storage disease have not been sufficiently rigorous. Since other forms of liver disease with hepatomegaly may closely simulate the picture,[20] we believe

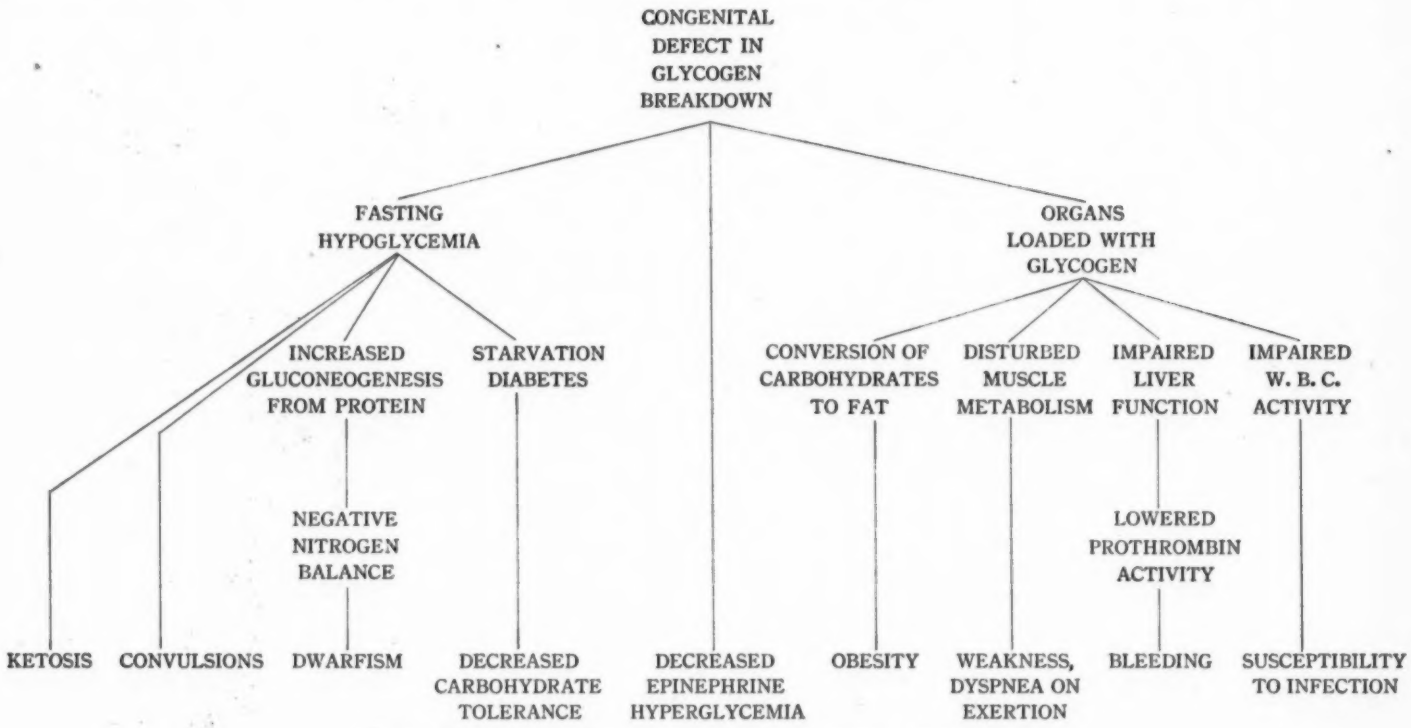

Fig. 2.—Diagrammatic outline of pathogenesis of glycogen storage disease.

a biopsy is justified in every case. The mere finding of an excessive glycogen content does not per se justify the diagnosis. The glycogen content should be maximal, namely, from 12 to 16 per cent, and its abnormal stability in vitro should be demonstrated. A number of cases reported in the literature as glycogen storage disease with concentrations of glycogen below 8 per cent have been atypical in other respects and should, we believe, be excluded from that category. High glycogen concentrations in the liver may be encountered after forced administration of carbohydrates or in cases of hyperinsulinism, but under such conditions the glycogen does not show the abnormal stability seen in cases of von Gierke's disease. The diagnosis can be further substantiated by demonstrating chemically that the liver contains a normal and not excessive amount of fat.

SUMMARY

Two cases of the hepatic form of glycogen storage disease (von Gierke's disease) have been studied in detail .

Observations on liver slices freshly removed at biopsy have shown an abnormal stability of the glycogen, but a satisfactory glycogenolytic response was obtained upon admixture with fresh normal liver, confirming previous work that the glycogenolytic enzyme system is defective in this condition. Liver slices treated with various enzyme preparations, including phosphorylase and amylase, gave results which were inconclusive as to the nature of the enzyme defect.

It was demonstrated that liver functions other than glycogenolysis may be affected in this disease, defective prothrombin formation and defective methylation being observed.

In one patient a pronounced lipemia was present at the age of 2 years which had almost completely disappeared at the age of 6 years, suggesting that the associated disturbance of fat metabolism, which has been observed repeatedly in infants with this disease, may be a self-limited one.

An unidentified reducing substance was found, probably belonging to the pentose group, in the urine of one of our patients.

Particular attention is called to two indirect results of the impaired glycogenolysis: (a) an abnormal conversion of carbohydrate to fat, demonstrated by respiratory quotient studies, which leads to obesity; (b) impaired nitrogen retention, brought about apparently by excessive gluconeogenesis from protein in the effort to sustain blood sugar, a condition which may interfere with normal growth. We have shown that this latter condition may be satisfactorily treated by the administration of an extra protein meal at night.

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SPINAL CORD TUMORS IN CHILDREN: A STUDY OF THREE CASES OF EPENDYMOMA

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WHILE spinal cord tumors in general have been the subject of a voluminous literature, those of childhood have attracted small attention. There have been wide discrepancies in the statistics on spinal cord tumors in children. In the earlier papers, spinal cord tumors were considered rare in childhood. Elsberg,[1] in 1925 reported in 100 cases only one case of spinal cord tumor in a child under 10 years of age. In the records of the Harriet Lane Home, only three cases were found out of 70,000 case histories. Stookey,[2] in 1928, reported eight cases in children under the age of 12 out of 165 spinal cord tumors operated on at the Neurological Institute.

Yet the older statistics from post-mortem records show a higher incidence in children. Horsley and Gowers,[3] in 1888 found out of fifty-eight cases, six, or 10 per cent, in children, and Schlesinger,[4] in 1898, out of 251 post-mortem cases, found thirty-three, or 13 per cent, in children under the age of 10 and twenty-seven, or 11 per cent, in children between the ages of 10 and 15. This discrepancy between post-mortem and operative groups suggested that spinal tumors have not been recognized readily in children during life and have been due, in part, to the lack of accurate diagnosis.[5]

In the more recent literature, Hamby,[6] in 1935, reported a total of 100 cases of spinal cord tumors in children collected from various sources up to that date. Elsberg,[7] in 1941, found five cases in children under 10 years of age and twenty-eight cases in the age group from 11 to 20 years, in his total series of 275 cases of tumors of the spinal cord.

Tumors of the central nervous system arising from ependymal cells have been looked upon as a rarity. The reports of those interested in tumors of the brain, reveal a small number of ependymal gliomas found in the brain. Bailey,[8] in 1927, reported only sixteen ependymomas of the brain out of 566 gliomas at the Cushing Clinic, and Fincher and Coon[9] reported only eight cases of ependymoma in 1929 out of 140 gliomas of the brain collected at the Barnes and St. Louis Children's Hospitals. Of the gliomas found in the brain, the ependymomas would seem, therefore, to constitute a rather small percentage.

With improvement in diagnosis and pathologic differentiation, the careful investigations of Kernohan, Woltman, and Adson,[10] on the other hand, showed

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that the incidence of ependymal tumors of the spinal cord was high and it constituted one of the most common tumors of the glioma group found in the cord. In an analysis of fifty-one intramedullary tumors of the spinal cord in 1931, twenty-one, or 42 per cent, were ependymomas. In 1940, Rasmussen, Kernohan, and Adson,[11] collected 557 cases of intraspinal tumors at the Mayo Clinic. Of these, ninety-five were gliomas, of which sixty-five, or 67 per cent, were ependymomas. In Elsberg's[7] series of 253 cases of intraspinal tumors reported in 1941, twenty-six were gliomas and, of these, twenty were ependymomas.

The literature on the incidence of ependymomas in children is meager. These reported series of intraspinal tumors were not broken down into age groups. Hamby,[6] in his series of 100 collected cases of spinal tumors in children, found twenty-three gliomas. However, these were not classified into types. Fincher and Coon,[9] in 1929, stated that ependymomas are the most commonly found central nervous system tumor of children but gave no statistics. In contrast to this, Ingraham[12] collected all the cases of tumors of the spinal cord in infancy and childhood since 1918 at the Children's Hospital in Boston and found only sixteen cases, none of which were ependymomas. Since Stookey[2] first emphasized the importance of spinal cord tumors in children in 1928, there has been very little further study and statistical analysis, despite the improvement in pathologic differentiation and diagnostic methods.

Ford,[13] in his book, *Diseases of the Nervous System in Infancy, Childhood and Adolescence,* has outlined the essentials in diagnosis of spinal cord tumors in children. In a child who has pain and muscle spasm of the back, with pain increased by coughing, sneezing, and straining at stool and at times becoming worse shortly after falling asleep, one must suspect a spinal cord tumor. In the majority of cases, he states that the first symptom is localized and persistent pain in the distribution of the dermatome supplied by compression of the affected nerve root. The presence of increased spinal fluid protein, xanthochromia, spontaneous coagulation of the spinal fluid, and obstruction of the spinal subarachnoid space as shown by the Queckenstedt test is further contributory evidence.

However, children with early signs of spinal cord pressure present difficult diagnostic problems and are usually incorrectly diagnosed, and spinal puncture is usually resorted to at a late date. Ingraham[12] has presented five cases of cord tumors that were diagnosed as poliomyelitis. Three cases of ependymomas in children are here presented, all of which were given an erroneous diagnosis. A review of these cases bring to light signs and symptoms which should be of benefit in more accurate diagnosis.

REPORT OF CASES

CASE 1.—Intramedullary ependymoma of dorsolumbar portion of spinal cord. Removal in two stages with marked improvement.

Clinic Record.—W. C., a white boy, 12 years old, was first seen in the Out Patient Clinic of the Los Angeles Children's Hospital, in November, 1940, with a history of rheumatism in the lower back and pain in the back of the knees for eighteen months. He was found to have a flat lumbar spine with all motion of the spine restricted. There was a 20-degree flexion contracture of the hips and a 10-degree flexion contracture of the knees. Roentgen examination of the dorsolumbar spine was reported as negative.

He was treated with massage, heat, and exercises. The urine analysis and blood picture were normal. Cholesterol determination was normal. A Wassermann was negative.

He was followed at monthly intervals in the clinic and despite physiotherapy, there was little improvement after eight months, with persistence of stiffness and pain in the lower back. He was then admitted to the hospital, July 15, 1941, for further study.

Hospital.—History taken in the hospital revealed that the boy had soreness of the lumbar region for two years which radiated to the back of both thighs and knees and was worse after walking and at night while in bed. He was treated by an osteopath for three months in an elastic strapping and with electric treatment, without any improvement. For about a year before admission, his back had been stiff.

Examination.—The essential physical findings were: (1) Slight stiffness of the neck manifested by inability to touch the chin to the chest; (2) absent knee jerks and diminished ankle jerks, no pathologic reflexes or clonus; (3) stiffness of the back with difficulty in bending, walked with a wide base; (4) moderate weakness of both lower extremities, no atrophy; (5) indefinite sensory level at fifth lumbar segment.

Laboratory Findings.—Urinalysis and blood picture were normal. Kahn, Wassermann, and tuberculin tests were negative. X-rays of the dorsolumbar spine were reported as negative. A spinal puncture revealed xanthochromic fluid which clotted on standing. There was a complete block on jugular compression.

Subsequent x-rays of the spine with lipiodol revealed a block at the level of the fourth lumbar vertebra.

Diagnosis.—A spinal cord tumor was believed to be present, the lowest portion at L4.

Operations: The first operation was performed July 23, 1941, by Dr. George H. Patterson.

An incision was made over the lower lumbar spine. The laminae of the third to the fifth lumbar vertebra were removed. The dura was opened and the entire lumbar area was filled with a soft gray tumor mass which shelled out easily. It was impossible to remove all the tissue along the fourth and fifth nerve roots. The incision was extended and the laminae up to the tenth dorsal vertebra were removed and similar tumor tissue dissected away. The upper pole of the tumor was not reached at this operation.

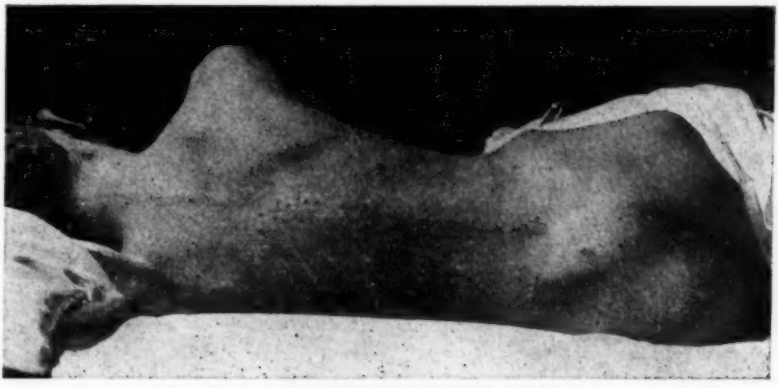

Fig. 1.—Extent of postoperative scar in Case 1.

On August 4, 1941, twelve days later, a second operation was done and similar tumor tissue, extending up to the eighth dorsal segment, was found compressing the cord, principally in the central portion. As much as possible was removed. Some still remained intimately connected to the cord and roots.

Course.—There were two short postoperative febrile courses. Shortly after the first operation, there was some numbness of the left arm. After the second operation, a paralysis of the left arm developed which improved slowly with physiotherapy. On the eighteenth day, after the second operation, deep x-ray therapy was begun and the patient received thirteen treatments over a five-week period. He was discharged Sept. 29, 1941, with only slight residual weakness of the left arm. (Fig. 1).

Pathology.—The specimen consisted of a number of pieces of soft cellular vascular grayish white tissue, the largest of which measured 3.5 cm. The cut surface was friable, cellular, and grayish pink. Histologically, the diagnosis was ependymal glioma.

Clinic Follow-up.—In November, 1941, three months postoperatively, the boy was seen in the Out Patient Clinic and marked improvement in muscle strength was noted. In January, 1942, he was asymptomatic, except for an indefinite sensory level at D6. In May, 1942,

all back pain was gone and the range of motion of the spine was considerably improved. In September, 1942, the patient was asymptomatic. His gait was normal and there were no sensory changes.

For the next three years he was followed at frequent intervals in the Out Patient Clinic and to date, three and one-half years postoperatively, there are no pathologic neurological findings. The reflexes are normal and the patient is symptomatically cured.

Comment.—Several interesting features stand out in the case. The patient had symptoms for one and one-half years before he was examined and his complaints were primarily pain and stiffness of the back. Flexion contractures of the knees and hips were present. The pain was worse at night. For eight months he was treated in the Out Patient Clinic without relief. A spinal puncture revealed xanthochromic fluid and jugular compression block. With surgery and x-ray therapy, this boy has been asymptomatic for three and one-half years, despite the fact that all of the tumor could not be removed.

CASE 2.—Ependymoma of cerebellum, medulla, and spinal cord. Biopsy taken. Tumor not removed. Patient died.

History.—F. A., a 4½-year-old boy, was first admitted Aug. 23, 1943, with a history of constipation for three days and a stiff neck for one day, occurring nineteen days before admission. At that time he was admitted to another hospital where the diagnosis of poliomyelitis was made. A spinal puncture at that time revealed clear, colorless fluid with a very occasional lymphocyte, no globulin, negative spinal Wassermann and a total protein of 57 mg. Culture of the spinal fluid was negative. He was given the Kenney treatment and subsequently transferred to the Children's Hospital for further treatment.

Examination.—Examination revealed slight weakness of the right arm and leg. There was spasm of the recti capitis muscles of the neck, the trunk muscles and the hamstrings. In the arms and legs, the deep reflexes were slightly more active on the left than on the right. The physical examination was otherwise negative.

Laboratory Findings.—Urine analysis was negative. Hemoglobin, 79 per cent; white blood count, 6,380; polymorphonuclears, 43 per cent; lymphocytes, 39 per cent; eosinophiles, 16 per cent; monocytes, 2 per cent. Roentgen examination of the dorsolumbar spine was reported as negative.

Course.—A diagnosis of postpoliomyelitis residuals was made and the Kenney treatment was continued with Kenney packs and muscle re-education for one month and the boy was then discharged.

Readmission.—A year later, Oct. 13, 1944, the boy was readmitted with a history of pain in the lower lumbar region for six months before admission. Four months before admission, he fell off a bicycle and injured his head. He vomited for several hours and was nauseated. X-rays of the skull taken by a private physician were negative. He was put to bed for a week. About two weeks after the fall, the backaches became worse and were only slightly relieved by massage. For the last month before admission, the back became very stiff and painful and sitting up became difficult and uncomfortable.

Examination.—The outstanding findings were a stiff neck and a very stiff spine. The patient was unable to bend forward and had difficulty rising to a sitting position when lying flat in bed. There was limitation of straight leg raising bilaterally. There were diminished knee jerks on the right and both ankle jerks were gone. There was no Babinski or clonus and no sphincter disturbances. A vague sensory level was present at D6. Later, he developed weakness of the left leg and also a foot drop.

Laboratory Findings.—Urine analysis was negative. Hemoglobin, 80 per cent. White blood count, 5,550; polymorphonuclears, 50 per cent; lymphocytes, 37 per cent; eosinophiles, 6 per cent; monocytes, 7 per cent. X-ray of the dorsolumbar spine was reported as negative.

Course.—Because of the persistence of stiffness of the neck and back, Kenney packs were reapplied to the neck, back, and hamstrings for a week, with no improvement. A spinal puncture was then attempted at L4 and L5. This was unsuccessful. Another spinal puncture was performed at L2 and L3. These were also dry taps. Subsequently, another spinal tap was performed under Seconal sedation. It was noted that the spine was still very stiff and did not relax under sedation. This was also a dry tap. Finally, Dr. George Patterson, did a spinal puncture under general anesthesia. Despite anesthesia, the rigidity of the spine did not relax and Dr. Patterson, after repeated attempts, obtained no spinal fluid although he was certain that he was in the spinal canal.

Diagnosis.—Because of repeated dry spinal punctures, this case was believed to be an intramedullary tumor, most likely an ependymoma.

Operation.—On Oct. 30, 1944, a laminectomy was performed by Dr. Patterson in the lumbar area, extending to the lower dorsal region. Upon opening the dura, the cord was found infiltrated with a soft tumor mass which filled the entire lumbosacral canal. It was impossible to remove the tumor or close the dura. The wound was closed after a biopsy had been taken.

Course.—Postoperatively, the stiffness of the back and neck appeared to relax somewhat. However, the boy developed strabismus and choked discs and he continued to go downhill. On the third week postoperatively, he received five doses of deep x-ray therapy within a week. His condition became progressively worse and he died Jan. 1, 1945, two months after operation.

Autopsy Findings.—Upon dissection, the spinal cord presented white friable globules of tissue which began at the terminal branches of the cauda equina and extended up the entire length of the cord to the brain. (Fig. 2). On the surface of the cerebellum small grayish white areas that averaged 3 to 4 mm. in diameter were present. Similar lesions were found over the base of the brain and roof of the third and fourth ventricles. The histologic examination revealed an ependymal glioma.

Fig. 2.—Infiltration of ependymoma in brain and spinal cord in Case 2.

Comment.—A 4½-year-old boy was mistakenly treated for poliomyelitis, and showed rapid progression of an ependymal tumor over a period of a year to involve the brain and the entire spinal cord. The outstanding features were a painful rigid spine which did not relax under anesthesia and repeated dry spinal punctures.

CASE 3.—Ependymoma of mid-thoracic region. Inoperable. Biopsy taken. Final result unknown.

Clinic Record.—B. J., a 13-year-old boy, was first seen in the Out Patient Clinic, Jan. 28, 1941, with a history of having bumped his back against a car door three months before. About a month later, he complained of pain in his back at night which would wake him up. The pain was worse upon lying down or sitting and was relieved by activity. The pain occasionally radiated down the right leg.

Examination.—Examination in the clinic revealed some limitation of forward flexion of the spine with the tips of the fingers reaching just below the knees. Tenderness was present over the seventh and eighth dorsal vertebrae. There was pain on forceful bending of the spine.

X-ray of the chest was negative for tuberculosis. X-ray of the spine revealed a soft tissue density at the lower dorsal vertebra suspicious of a tuberculous abscess. A tuberculin test with 0.1 mg. was strongly positive. The boy was then admitted to the hospital with a diagnosis of tuberculosis of the spine on Jan. 30, 1941.

Hospital.—History taken in the hospital revealed that following the injury by the car door to his back, the boy developed pain in the upper thoracic region. In the last month before admission, the pain was more intense in the lower back. He also noted some numbness of the right leg for the last three months, as though it were asleep. The back pain was accentuated by coughing, straining, or sneezing. He would hold his nose to prevent sneezing because the back pain then became so severe.

The family and past history were noncontributory. There was no history of any tuberculous contact.

Examination.—Examination revealed a somewhat undernourished boy, not acutely ill. There was no stiffness of the neck, but forward movement caused pain in the lower back. There was some stiffness of the lower back and hypesthesia in the sensory distribution of L5, S1, and S2, most marked in the right leg. Some atrophy was present in both calves. The deep reflexes in the arms and legs were equal and active. The abdominal reflexes were absent on the right. No pathologic reflexes were present. Palpation of the spine elicited tenderness in the middorsal region.

Laboratory Findings.—Urine analysis was negative. Blood picture was normal. Kahn and Wassermann were negative. The sedimentation rate was 4 mm. per hour.

Course.—The diagnosis of tuberculous abscess of the spine was made at first by the consulting pediatrician. The patient was placed on a Bradford frame for two weeks. However, because the boy was unruly and uncooperative, a body cast was applied on Feb. 18, 1941. On Feb. 23, 1941 atrophy and weakness of the left leg were noted with absence of the ankle jerk on the left. These findings were then believed to resemble that of an old poliomyelitis and their relationship to the previous findings was not definite.

On Feb. 24, 1941, a spinal puncture was done and revealed one cell, normal pressure, no block on jugular compression and a total protein of 570 mg. The fluid was straw colored and the Pandy was 4 plus. The spinal puncture was repeated the following day. The dynamics were normal, with a pressure of 100 mm. Three cells were present, the total protein was 486 mg. Four cubic centimeters of lipiodol were instilled. X-rays with lipiodol revealed a persistent block at the seventh dorsal vertebra.

Diagnosis.—The child was believed to have a spinal cord tumor at the seventh dorsal vertebra.

Operation.—Performed on March 6, 1941, and a laminectomy was done from D5 to D7. Operation was performed by Dr. David L. Reeves. The dura over the fifth to the seventh thoracic region was opened and a tumor mass, slightly bluish in color with increased vascularity was encountered. The tumor was found to be infiltrating the cord and could not be removed. A biopsy was taken. The dura was left open for decompression and the wound closed.

Course.—Postoperatively, there was improvement in the strength of the left leg and decrease of pain in the back. The wound healed and the patient was temporarily symptomatically improved. He received no x-ray therapy.

This patient had always been a difficult behavior problem and unmanageable during his convalescence. Finally, he was discharged against medical advice, on April 2, 1941, and was last heard of on June 3, 1941, through a social service contact note which stated that he had developed recurrence and severe pain in the back and was unable to stand.

Pathologic Findings.—The gross specimen consisted of a soft piece of semitransparent grayish pink tissue which had the histologic appearance of an ependymal glioma.

Comment.—A 13-year-old boy had pain in the back for three months which was worse at night and aggravated by sneezing and coughing. A positive tuberculin test and some stiffness of the back suggested tuberculosis of the spine. Later, the diagnosis of residuals of poliomyelitis was considered. Spinal puncture revealed an elevated total protein and lipiodol confirmed the diagnosis of a spinal cord tumor.

DISCUSSION

In reviewing our three cases, several important symptoms predominate. By far the most constant and striking symptoms are the presence of pain and stiffness of the back. The pain is variable, slowly progressive and becomes worse at night. It may be aggravated by coughing and sneezing. The stiffness of the

back is persistent and does not respond to conservative treatment. In one case, the stiffness was so severe that it did not relax even under general anesthesia. In two cases, there was a history of trauma. The neurological findings were not dependable or diagnostic. The spinal fluid in all three cases showed either increased protein, xanthochromia or complete block.

The finding of pain and stiffness of the back is mentioned by other investigators. Stookey[2] found pain in the lower back and weakness of the lower legs as common symptoms in his group of intramedullary tumors in childhood. In our cases, some degree of weakness of the lower extremities was evident at some time during the course of the disease. Cushing[15] in reporting a case of ependymoma of the cervical cord in an 8-year-old girl, found the most striking sign objectively to be a curious fixed rigid position of the head which resisted any attempts at manipulation.

Fig. 3.—Compression of pedicles in Case 1. Lipiodol also visible.

The dissociation of sensory loss with loss of pain and temperature and preservation of touch as described by Cairns and Riddoch[14] in intramedullary tumors, was not seen in these cases.

Operations were performed on all three cases. Two were found to be inoperable. In one case where surgical removal was possible, followed by adequate x-ray therapy, the boy is still alive and asymptomatic after three and one-half years. It is evident from the case histories that the rate of growth of ependymomas is variable. Early diagnosis and operative intervention may improve the ultimate prognosis. A spinal puncture is recommended early in all cases of stiffness and intermittent or persistent pain of the back in children where the diagnosis is doubtful. The surgical treatment of ependymal gliomas and the status of x-ray therapy is discussed in detail by Adelstein and Patterson.[16]

In retrospect, upon reviewing the x-rays of the spine, it was found that all three cases showed definite changes in the pedicles, characterized by flattening or compression of the normal convex curve on the inner aspects. In Case 1 the pedicles of L1, L2, and L3 were markedly flattened bilaterally and the convex curve which is normally present, became concave (Fig. 3). In Case 2, the pedicles of L1 and L2 on the right were narrowed and their convexity was less than on the left. In Case 3, similar changes were noted in the pedicles of L2 on the right. These changes were constant in all films and were not due to rotation.

Dyke[17] in Nelson's *Diagnostic Roentgenology* says that, "alterations in the pedicles due to tumors are so common that it is advisable to describe their normal appearance. In films taken in the anteroposterior view, the shape of the pedicles is usually more or less oval. In the cervical region, the pedicles appear narrow, while in the lumbar region, they are almost circular. In the former region, the mesial border of each pedicle varies from flat to convex, while in the thoracic and lumbar segments of the vertebral column, the internal borders of the pedicles are usually convex, although there are frequent exceptions. The frequency with which these exceptions occur makes it unwise to base a diagnosis of a spinal cord tumor solely upon the existence of flat or concave pedicles. In children, the mesial borders of the pedicles cephalad to the 7th thoracic vertebra are commonly concave."

In ependymomas "the pedicles of a number of vertebrae are flattened and they may be concave, and the interpediculate measurements of the affected segments are considerably increased."

Charts with interpediculate measurements were done by Dr. R. G. Karshner for Cases 1 and 3. In Case 1, the measurements exceeded the normal variation at L2 according to the chart of Elsberg and Dyke.[18] In comparing the interpediculate measurements made on the x-rays taken in the hospital preoperatively and those made on the x-rays in the Out Patient Clinic eight months previously, there is definite increase of three to four millimeters in D12, L2, L3, and L4 segments, although they do not all exceed the normal range on Elsberg and Dyke's chart. In Case 3, the interpediculate measurements fell within normal range. Yet it must be remembered that these so-called normal measurements of Elsberg and Dyke's chart were for patients over 12 years of age and primarily of adults and so cannot be accurately applied to those of children.

SUMMARY

Three cases of ependymal gliomas in children are reviewed which were incorrectly diagnosed at first and treated without improvement for variable lengths of time. Pain and stiffness of the back, slowly progressive and usually worse at night, were prominent symptoms. Some degree of weakness of the lower extremities was evident at some time during the course of the disease. A spinal puncture was found to be the most important diagnostic procedure and is recommended early in all cases of stiffness and intermittent or persistent pain in the back in children, where the diagnosis is doubtful. Usually, this has been done too late.

Compression of the pedicles, when present on x-ray examination, is a valuable contributory finding.

Surgical removal should be attempted, in the face of extensive involvement, since improvement can be obtained even if not entirely removed. One of these patients is still alive and asymptomatic three and one-half years postoperatively.

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ADRENOGENITAL PSEUDOHERMAPHRODITISM TREATED WITH STILBESTROL

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PSEUDOHERMAPHRODITISM is only a relatively rare entity but always provokes considerable comment when it occurs. Determination of the true sex of the individual is an intricate problem, and treatment of the condition allows imaginative speculation ranging from various operative procedures to the administration of specific hormones. Estrogenic substances have been used a few times in efforts to cause demasculinization and feminization of female hermaphrodites. In the particular case to be reported here, stilbestrol was used with such intent. Although the clinical results were not altogether successful they do illustrate the desirable and undesirable effects as well as the limitations of the use of estrogens in comparable situations. Aside from these considerations, the following patient is sufficiently interesting to warrant testimony.

The patient was first observed at the University Hospital in February, 1942, and at that time was 5 years old. The parents had never been certain of the true sex of the child, since the genitalia were not characteristic of either the male or female, but "she" had been reared as a girl. The child had been growing at an abnormally rapid rate. At the time she came to the hospital her height was 49.3 inches and her weight 62.7 pounds (average measurements for 7½ years). An older sibling, whose sex had also been in doubt and who had grown rapidly, had died of pneumonia two years previously at the age of 6 years. An autopsy of this sibling was reported to have revealed marked hypertrophy of the clitoris, an infantile uterus, normal ovaries, a fully developed vagina, and definite diffuse hyperplasia of both adrenal glands.

Physical examination of the patient under discussion was essentially normal except for the large size of the child, the tendency toward a masculine physique, and the appear-

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ance of the genitalia. There was a large amount of pubic hair, female in pattern. The phallus measured 2.5 inches in length and had a definite glans and prepuce but no urethral opening. The latter was found to be just below the phallus, in a completely hypospadic position. There were well-developed labia present. No testicles could be palpated. The vaginal orifice was small and partially obliterated by a membrane.

Visual field examinations and roentgenograms of the skull were normal. Intravenous pyelograms showed no abnormalities of the urinary tract. A twenty-four-hour urine sample yielded 22 mg. equivalents of crystalline androsterone (normal from 4 to 8). Subsequent determinations were also consistently elevated. An exploratory laparotomy was

Fig. 1.—Appearance of patient at the time of her first admission to the hospital, age, 5 years.

performed and showed the presence of normal tubes and ovaries, a rudimentary uterus, and generalized enlargement of both adrenal glands. One-third of one adrenal gland was removed and microscopic section revealed diffuse hyperplasia of the cortex. A diagnosis of adrenogenital female pseudohermaphroditism was thus established.

In an effort to reduce the masculinizing effect of the adrenal gland roentgen therapy was employed (600 r.u. to each gland). After an interval of two months there was no appreciable change in the patient's appearance or in the size of the clitoris. With the

same goal of demasculinization in mind oral stilbestrol was then started. After four months of estrogen therapy, 5 mg. daily, definite changes were noted. The breasts had become developed and the nipples pigmented. Axillary hair had appeared for the first time. The clitoris, however, had not changed measurably in size. Since the patient was complaining of some toxic symptoms, the dose of stilbestrol was reduced to 3 mg. daily. The patient was observed again after another interval of four months, but no new changes were seen. The stilbestrol dosage was then reduced to 2 mg. a day. At the end of six

Fig. 2.—Appearance of the genitalia before therapy was started.

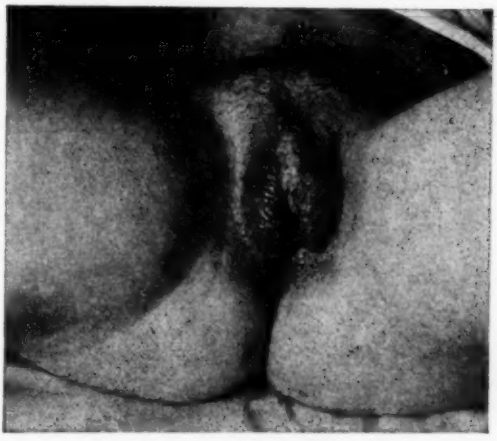

Fig. 3.—Appearance of the genitalia after plastic operations had been performed. Some postoperative edema is still present.

more months the parents reported that the girl was no longer growing at an accelerated rate and that the clitoris had become slightly shorter. Actually, at this time it measured 1.7 inches, a reduction of 0.75 inches. Plotting of the height and weight of the patient (54 inches and 81 pounds) also corroborated the impression that she had grown at a normal rate since her last visit. Ten months later the child was once more examined. She now had the appearance of an adolescent girl except for the hirsutism of the legs and the still enlarged clitoris, measuring 1.25 inches.

Estrogen therapy was discontinued at this time because roentgenograms showed that the epiphyses were nearly closed. It was felt that the stilbestrol might be contributing

to the precocious bone maturity. In order to prepare the girl for a more normal female adult life and to put an end to the embarrassments which she was experiencing because of the enlarged clitoris, plastic operations were performed in November, 1944. These consisted of an amputation of the clitoris and an extension of the vaginal orifice. The cosmetic result of these procedures is recorded in Fig. 3. It is expected that the girl will be capable of performing coitus, but it is doubtful whether the uterus will ever be mature enough to support menstruation or pregnancy.

COMMENT

The great majority of pseudohermaphrodites are of the adrenogenital type. Hyperplasia or adenomas of the adrenal cortex bring about profound changes in the development of the individual and in the sex characteristics. When such lesions are congenital the result is pseudohermaphroditism. When they develop in early childhood they produce precocious puberty, while in adult life the resulting symptom-complex is termed virilism. Hyperplasia of the cortex causes marked acceleration of body growth and heterosexual characteristics. The latter is manifested in the female by hirsutism of male or female distribution and hypertrophy of the clitoris.[1] Animal experimentation indicates that such congenital anomalies may be due to antenatal endocrine dysfunction in the mother. If the mother animal is treated with male hormone during pregnancy, the female young show externally a male habitus with a clitoris resembling a penis. The ovaries are normal and the tubes and uterus are more or less completely formed. The distal part of the vagina is usually missing.[2] In view of these observations, it is worth recording here that the androgen excretion of the mother of our patient was determined and was found to be normal in amount.

Young[3] collected a series of eight female pseudohermaphrodites in three of whom adrenocortical hyperplasia was demonstrated by laparotomy. Partial resection of the cortex of each was performed. Young described the results as being "fairly satisfactory," but diminution of masculine characteristics occurred in only one of the patients. This author used endocrine therapy in two cases in an effort to cause menarche, but in both instances the treatment was unsuccessful. Lisser[4] administered stilbestrol to a female pseudohermaphrodite to cause feminization and demasculinization with somewhat the same success as we have had in our patient. The estrogen, 1 mg. three times a week given parenterally, caused breast development, some diminution in the size of the clitoris, and disappearance of hirsutism. The onset of menstruation also occurred during the administration of the hormone. This girl was nearly 17 years old when stilbestrol was given so that its effect on her growth was negligible.

The benefits derived from the use of stilbestrol in our patient were disappointing. Undoubtedly it accentuated the female secondary sex characteristics. The effect on the clitoris was only a minimal reduction in size. The effect on the growth of the child is difficult to evaluate. The growth rate of the patient was normal for the interval during which she received medication although it had been rapid before that time. The age at which closure of the epiphyses would have occurred if stilbestrol had not been given is unestimable. Young did not give the heights of his patients. Lisser's patient, who had had no estrogen therapy until she was past the growth period, attained a height of only 56 inches. Our patient has reached nearly this same height. Bone age determinations* before and after endocrine therapy showed no acceleration of the bone ages. The bone age one year before therapy was started

*Taken from Todd, T. W.: Atlas of Skeletal Maturation, St. Louis, 1937, The C. V. Mosby Company, pp. 178, 186, 194.

was ten years, three months. At the time therapy was begun it had become twelve years, six months, and after two years of stilbestrol administration it was fourteen years, an advance of only one and one-half years during the two-year period of therapy. This would seem to indicate that the hormone did not in this case cause the premature epiphyseal closure and that the adrenal abnormality caused not only an accelerated growth rate but also terminated the growth process earlier than normal. Reilley and associates,[5] in their article reviewing the subject of pseudosexual precocity, arrived at a similar conclusion. They stated that "the early appearance of sexual characteristics hastens ossification and epiphyseal closure, and, as a result, these children . . . are likely to cease growing prematurely and be relatively short in maturity." On the other hand, it has been shown in many other instances that estrogens, when administered to children, do cause early closure of the epiphyses. Consequently, the stilbestrol was discontinued to give the girl every chance to reach her maximum height. When the patient becomes 15 or 16 years old and it is psychologically more desirable for her to have well-developed sex characteristics, estrogen therapy may again be indicated.

SUMMARY

A patient who has adrenogenital pseudohermaphroditism is reported. The attempt which was made to demasculinize this patient by the administration of stilbestrol and the results of this attempt are discussed.

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KERNICTERUS: NEUROLOGICAL SEQUELAE OF ERYTHROBLASTOSIS FETALIS

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IT HAS long been known that there is a definite relationship between jaundice of the newborn and pigmentation and degeneration of the nerve cells of the brain—particularly the basal ganglia. Recent advances in the study of jaundice of the newborn, specifically of the Rh factor and its diagnostic and therapeutic application in erythroblastosis fetalis, have led to a marked increase in the survival rate of newborn infants with jaundice. This fact makes of increasing significance the prognosis of these patients, particularly in regard to the development of cerebral lesions. It is the purpose of this paper to review the prevailing knowledge as to the relationship of jaundice of the newborn and so-called kernicterus and to present further clinical data pertaining to the prognosis of erythroblastosis fetalis as regards pathology of the central nervous system.

From The Children's Memorial Hospital.

Kernicterus as a pathologic entity was first described by Orth[1] in 1875. The term kernicterus was coined by Schmorl[2] in 1903 to designate jaundice of various nuclear masses of the brain. The structures most commonly affected are the caudate, lenticulate, subthalamic, and dentate nuclei, the thalami, the mammillary bodies, the cornua Ammonis, the nuclei of the cranial nerves, the olives and even parts of the cerebellar cortex, as well as the anterior and posterior horns of the spinal cord.

Relatively few autopsy reports on this condition are available. Thus, Schmorl found but six instances of kernicterus in 120 cases of jaundice of the newborn that came to autopsy. There is, however, a striking similarity in all of those cases described, and the conclusions to be drawn from these reports were well summarized by Zimmerman and Yannet[3] in 1933: "(1) Kernicterus is not a disease in itself, but occurs as one of the lesions that may be found in newborn infants with severe jaundice, and only in comparatively few of these. (2) This lesion has never been observed in adults; there are no reports of its resulting from jaundice other than that of the neonatal period. (3) It is most frequently, if not exclusively, associated with icterus gravis neonatorum. Obstructive jaundice has yet to yield an instance of kernicterus." FitzGerald, Greenfield, and Kounine[4] take issue with this last statement, and quote Pasachoff as recording a case associated with obstruction of the bile passages, and Biemond and Van Creveld as reporting two cases associated with neonatal septic hepatitis. Pasachoff's[5] report, however, although associated with congenital atresia of the bile ducts, makes plain to state that there was also strong evidence of erythroblastosis fetalis in that the liver, spleen, kidneys, adrenals, and lungs showed extensive hematopoiesis and the peripheral blood contained 40 per cent erythroblasts. This author states that in his opinion the kernicterus was related to the icterus gravis neonatorum and that the atresia of the biliary system was coincidental. He also noted cerebral aplasia with the cortex of the frontoparietal region being aplastic and replaced by large cysts with a thin, fibrous-tissue covering.

Biemond and Van Creveld[6] at the University of Amsterdam described in detail two cases of neonatal jaundice in which typical pathologic findings of kernicterus were proved at autopsy, and in which it was further shown that death was due to umbilical sepsis with no relationship to erythroblastosis fetalis. It is of interest to note that in both of these cases there was developmental hypoplasia of the corpus callosum and fornices of the brain. No other instances of kernicterus unequivocally occurring with jaundice other than from erythroblastosis have been found. It can still be stated, therefore, that no cases of kernicterus associated solely with obstructive jaundice have been reported.

Many theories have been advanced as to the production of the cellular pigmentation of kernicterus. Orth stated that there was a primary necrosis of parts of the brain, and these parts subsequently took on icteric pigmentation. Schmorl also found that in degenerated zones of the brain there was concentration of pigment; he believed the necrosis to be due to vascular damage caused by some toxin or by thrombosis. In 1907 Beneke[7] summarized the prevailing views concerning the relation of cerebral injury to the pathogenesis of kernicterus as follows: "(1) A peculiar attraction of bile pigments for ganglion cells. (2) Primary damage of ganglion cells by substances such as bile salts with secondary cellular pigmentation. (3) Ganglion cell damage by ischemia or trauma and subsequent pigmentation of these cells."

More recently Spielmeyer[8] has investigated the blood supply of different brain structures. He concluded that the basal ganglia, chiefly the corpus striatum and cornu Ammonis, have a relatively poor blood supply and might well be expected to suffer first in diseases accompanied by anemia or affecting the blood supply to the brain.

It has been shown that these same basal ganglia normally have a rich iron and calcium content and are the regions most commonly injured in anemia of the brain whether it be from carbon monoxide, carbon dioxide, or morphine poisoning. Further relatively recent evidence has been presented in favor of the view that a predisposing factor in the localization of these lesions may be maldevelopment of the brain. As cited earlier, Biemond and Van Creveld reported a lack of normal development in their two cases of kernicterus, and other authors have indicated similar developmental abnormalities. The most tenable hypothesis at present, therefore, seems to be related to an increased susceptibility to ischemia of the areas involved with secondary staining by the bile pigments. The primary existence of some degree of maldevelopment may be a contributory factor to the ischemia.

The almost universal association of kernicterus with erythroblastosis fetalis would suggest a more specific etiological factor in the production of kernicterus than can be explained merely on the basis of ischemia and jaundice, even with some maldevelopment. Experimentally, it has been thus far impossible to reproduce in animals the pathologic picture of kernicterus. It may be that the anti-Rh agglutinins have a specific affinity and toxic action on the cells of the basal ganglia or in some way sensitize these cells to the circulating bile pigments.

Pathologically the important lesion is a demyelinization and degeneration of the nerve cells, the pigmentation being of secondary importance. Although macroscopically the pigmentation is greatest in the nuclear structures of the brain, microscopically cellular degeneration and pigmentation can be found scattered throughout the cerebral and cerebellar cortices. De Lange[9] has adequately demonstrated that the areas of most marked pigmentation are not always those of most marked degeneration. In a patient 3 years of age examined at autopsy by Zimmerman and Yannet[10] all of the criteria for kernicterus were present, both clinically and anatomically, except the pigmentation, which evidently had faded as jaundice anywhere fades during the course of time.

The term kernicterus is being used to describe not only an anatomic pathologic lesion, but also the clinical manifestations of this lesion as observed in the living patient. If the patient survives the neonatal period there develops immediately, or weeks or months later, evidence of damage to the basal ganglia, that is, extrapyramidal spasticity, athetoid and choreiform movements, and emotional instability plus more or less marked mental retardation.

In 1937, Klingman and Carlson[11] from the Department of Corrective Motor Education at the Neurological Institute of New York, reviewed the birth and neonatal histories of 675 children with all forms of neuromuscular dysfunctions. They found forty-five with a definite history of severe jaundice early in life. It was impossible to make a diagnosis of erythroblastosis at the time the study was made, but thirty-eight of the forty-five were jaundiced at birth, three on the first day, one on the second, and one on the third day. In seventeen cases the jaundice persisted for two weeks or longer, an average of ten weeks. Symptoms of disturbance of the nervous system in the form of convulsions, spasticity, apathy or lethargy, restlessness, increased crying, or difficulty in feeding were present in twenty-eight of the forty-five and accompanied the jaundice. In the remaining cases symptoms referable to the nervous system were not recognized

at the time of the jaundice but appeared weeks or months later. The symptoms then appeared in the nature of delayed motor functions, gradual progressive spasticity, incoordination, choreoathetosis, ataxia, hypotonicity, or retardation of mental development. Almost all of the cases showed definite mental impairment.

At The Children's Memorial Hospital there were available for this study thirty-four cases of jaundice of the newborn. Clinical records were reviewed back to 1937, while autopsy records were reviewed back to 1920, and those diagnosed pathologically as kernicterus are included in this study. Of these thirty-four cases, twenty are considered to be erythroblastosis fetalis. This diagnosis has been made by clinical study, laboratory data, and autopsy findings. In fifteen of the twenty cases a definite diagnosis has been made from clinical study confirmed by the proper Rh factors in mother and patient (that is, Rh-negative mother and Rh-positive patient). Of the remaining five, three were not available for Rh testing. These three were patients who expired and were examined at autopsy prior to 1943. These case histories follow.

J. F., a white male, was born Feb. 4, 1930. Both parents were in good health. There were two siblings aged 2 and 4; both were in good health and had no history of jaundice at birth. The mother had had no miscarriages. The patient was born at full term by normal, spontaneous delivery with no cyanosis or other difficulty. There was no jaundice noted at birth; the jaundice was first noticed twenty-four hours after birth. The patient was admitted to The Children's Memorial Hospital at the age of 60 hours at which time a marked degree of jaundice was noted. Pupils were equal and regular, the sclerae markedly jaundiced. Heart and lungs were normal. The spleen was easily palpable, extending medially to the nipple line and inferiorly to the umbilicus. The liver edge was just palpable below the right costal margin. Urine was dark brown and contained bile. Stools were dark and contained bile. Blood count showed a hemoglobin of 40 per cent, 2,960,000 red blood cells per cubic millimeter, and a total of 172,000 white blood cells and nucleated red blood cells; a differential count revealed 78.5 per cent normoblasts, 1.5 per cent erythroblasts, and 0.9 per cent proerythroblasts, the remainder being divided among the lymphocytic and myelocytic series. The patient was given intramuscular blood, 15 c.c. into each buttock, but he gradually developed respiratory difficulty and expired twelve hours after admission. Autopsy findings were compatible with a diagnosis of erythroblastosis fetalis and serial sections of the brain showed an icteric discoloration of the nuclei of the columns of Goll and Burdach and the olivary nuclei. Microscopic examination of the brain was not available.

A. D., a white male, was born July 19, 1935. He was the youngest of three children born of normal, healthy parents. Both preceding siblings were alive and well. The last trimester of pregnancy was marked by strong pseudocontractions of the uterus, but there was no evidence of maternal toxemia. During the last two weeks fetal activity was markedly reduced. Delivery was spontaneous and noninstrumental; labor was not prolonged. Birth weight was 6 pounds, 7 ounces. The baby's appearance was normal except for some pallor and icterus. He was put to breast but did not nurse well. Because of general apathy and increasing icterus he was seen by Dr. Joseph Brennemann. At this time the patient showed a marked generalized icterus. The spleen and liver extended ½ inch below the costal margin. The hemoglobin was 50 per cent, red blood cells numbered 3,600,000 per cubic millimeter, and a smear showed many young red cells. Wassermann test was negative. During the first ten days of life, 250 c.c. of whole blood was given intravenously. During this period the child either nursed or was given his mother's milk by dropper. On the fourteenth day twitching movements of the left eye and of the arms were noted, but these were not severe. The child was discharged home on the fourteenth day weighing 6 pounds, 13 ounces. He stayed at home for three weeks during which time he gained 11½ ounces and became increasingly alert and active. At this time there was noted a radical change in the baby's condition—there was increasing pallor and stupor. Examination on readmission showed a jaundiced, semistuporous infant with a bulging fontanel, an abnormal Moro reflex, unequal pupils, an inconstant nystagmus, and weakness on the left side. Convulsions began and the patient expired twelve hours after this second admission.

Autopsy revealed ectopic foci of erythropoiesis in the liver, spleen, thymus, and lymph nodes—a diagnosis compatible with erythroblastosis. There was a massive intracranial hemorrhage over the right cerebral hemisphere and within the right ventricle to account for the sudden death. The surface of the brain also showed a piebald golden greenish discoloration which is suggestive of kernicterus. More detailed brain studies were not made.

B. Mc., a white female, was born July 6, 1942. The mother had had three previous pregnancies. The first child was normal. The second child lived several days and was very jaundiced, dying suddenly. The third child was normal. The present child was born at term after an uneventful pregnancy; the birth weight was 6 pounds, 7 ounces. She cried immediately and her color was good. Five hours after birth jaundice was noticed and the blood count was as follows: 3,300,000 red blood cells per cubic millimeter, 86 per cent hemoglobin, and 24,600 white blood cells per cubic millimeter with 79 per cent polymorphonuclear leucocytes, 12 per cent lymphocytes, 9 per cent monocytes, and 6 per cent normoblasts. A transfusion of 80 c.c. of blood (not from the mother) was given, and another of 60 c.c. was given twenty hours after birth. The patient died very suddenly about sixty-five hours after birth.

The autopsy revealed multiple foci of erythropoiesis in the liver and spleen and evidence of young red cells in other tissues of the body. These findings are compatible with erythroblastosis fetalis. The brain sections showed a bright yellow discoloration of the basal ganglia. This was symmetrical and affected the thalamus and the globus pallidus. This bright yellow color was present after five weeks in formalin and is highly suggestive of kernicterus. Microscopic examination of the brain was not done.

The remaining two patients who are being considered clinically as having erythroblastosis fetalis have the following histories:

S. C., a white female, was born Jan. 9, 1944. Both parents were in good health. The patient is the fourth child. The oldest sibling, who was jaundiced at birth, at 10 years of age was in good health. The second sibling was also healthy at the age of 9 years. The third sibling died at birth of hydrocephalus, but with no jaundice. S. C. was born after a nine-hour labor with cephalic presentation and by a rapid delivery with signs of fetal distress. She was cyanotic, and was resuscitated by tracheal aspiration and mouth to mouth breathing. She was given oxygen and placed in an incubator. Her birth weight was 7 pounds, 15 ounces. Twenty-four hours after birth a deeply icteric tint was noted in the sclerae, mucous membranes, and skin. The spleen was palpable 2 inches below the left costal border and the liver 1 inch below the right costal border.

The patient was admitted to The Children's Memorial Hospital with a blood count of 5,020,000 red blood cells per cubic millimeter, a hemoglobin of 16 Gm., and 28,200 white blood cells per cubic millimeter, the smear showing 23 per cent nucleated red cells. She was reported as Rh negative, the mother as Rh positive, and the father as Rh positive—readings being equivocal. The icterus index was 236. Fifty cubic centimeters of Rh-negative blood from a compatible donor was given intravenously and repeated two days later. In spite of these two transfusions, on the fifth hospital day the red blood cell count was 1,800,000 per cubic millimeter and the icterus index 520; the patient's color corresponded to this icterus index.

Because of the controversial and atypical Rh determinations, blood from the parents and patient was sent to Dr. Israel Davidsohn at Mt. Sinai Hospital who kindly did the studies and reported all three samples to be Rh positive. However, the patient's blood did contain anti-Rh agglutinins of an atypical type and Dr. Davidsohn classifies this patient as an atypical case of erythroblastosis fetalis.

The urine and feces both contained bile, fragility tests were normal, van den Bergh's test was positive both direct and indirect, and the cephalin flocculation test was negative. There was no evidence of a blood dyscrasia other than erythroblastosis and no evidence of other cause for jaundice.

During her stay in the hospital the patient was given six transfusions of Rh-negative blood, totalling 300 c.c. She remained in the hospital for three months during which time her icterus subsided; at discharge the icterus index was 18, and she weighed 8 pounds, 9 ounces. Neurological examination at this time revealed some spasticity of the legs, more marked on the left. Since discharge she has been followed in the clinic and has steadily gained weight and completely lost her icteric color. At the age of 11 months she weighed 21 pounds, 8 ounces. She was examined in the neurology clinic where it was noted that the spasticity of the legs was gone, and that there were no pathologic neurologic findings. At the age of

11 months she was not yet able to sit up alone but otherwise was apparently normal. Enough time has not yet elapsed to evaluate adequately any permanent cerebral damage or mental retardation liable to result from such an extreme icterus in a case of erythroblastosis fetalis.

Both parents and this patient were Rh positive. Levine[12] reporting 350 mothers of infants having erythroblastosis found that 10 per cent were Rh positive; of 204 husbands 100 per cent were Rh positive; and of 138 affected infants 100 per cent were Rh positive. From these studies he concluded that 10 per cent of the mothers having babies with erythroblastosis are atypical, and the pathologic findings are due to "atypical" blood factors not determined by the standard Rh tests. It is justifiable, therefore, because of the clinical symptoms and history and in view of the blood studies carried out by Dr. Davidsohn to include this patient as a representative of the expected 10 per cent atypical cases.

The fifth patient was a 13-year-old boy who was markedly jaundiced immediately following birth. He was a first child born after a nine months' gestation by normal delivery with no cyanosis or other signs of neonatal distress. His birth weight was 8 pounds, 9 ounces. He was jaundiced for six weeks. When he was 11 months of age it was first noticed that he did not sit up. From that time on he was noted to be spastic, athetotic, and retarded mentally. More details of this neonatal period are not available. The mother is Rh positive and the patient is Rh negative. The long period of neonatal jaundice not associated with obstruction and followed by sequelae in the central nervous system is very suggestive of an atypical erythroblastosis fetalis and a severe kernicterus. The inclusion of this patient as the second atypical case in twenty is still within the expected 10 per cent of atypical cases of erythroblastosis fetalis.

Of these thirty-four cases of jaundice of the newborn studied, fifteen are diagnosed as having some of the manifestations of kernicterus. Where the clinical manifestations were not obvious the diagnosis was confirmed by examination by a child neurologist. Of these fifteen cases, seven were diagnosed pathologically by autopsy and direct examination of the brain. Six of these are included in the nineteen cases of erythroblastosis fetalis, three were in the group with confirmatory Rh factors, and three in the group in which no Rh testing was done. The seventh case is an extremely interesting one:

B. H., a white male, was born Jan. 1, 1940, after an uneventful pregnancy of nine months' gestation. Delivery was normal. The birth weight was 6 pounds, 11 ounces. The infant had good color, cried spontaneously, and nursed well. Physical examination at birth was normal. On the fourth day of life the skin and mucous membranes became deeply icteric and pitting edema developed over the lower half of the body. On the fifth day the liver and spleen became palpable. The stools were always well colored; the urine became dark on the fourth day. The hemoglobin was 130 per cent, red blood cells numbered 5,630,000 per cubic millimeter, and white blood cells 11,400 per cubic millimeter with 59 per cent polymorphonuclear leucocytes, 34 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles. The patient became limp and had periods of cyanosis with shallow respirations. Twitchings of the face and arms were noted. Convulsive twitchings increased and periods of cyanosis became more frequent. The infant expired on the eighth day of life.

Autopsy failed to reveal any ectopic foci of erythropoiesis in the liver, lung, spleen, or any other organs. The only indication that this might be an erythroblastosis was the deposition in the Kupffer's cells of the liver of coarse confluent masses of a greenish brown or golden brown pigment which gave a markedly positive reaction for iron with the Prussian blue stain; this was noted as a heavy deposit of hemosiderin in the Kupffer's cells. Cut section of the brain after fixation revealed a relatively normal architecture and coloration of the cortex, as contrasted with the following: an intense, bright, canary yellow, sharply defined discoloration of the thalamus, the lentiform nucleus, the hypothalamic nucleus, the mammillary body, Ammon's horn, the dentate nucleus of the cerebellum, the olivary nucleus of the medulla oblongata, and the cerebellar cortex of the flocculus. Microscopic examination of these structures revealed widespread, although mild but definite, fragmentation of the tissue and some vacuolization. The ganglion cells were swollen, cloudy, and had indistinct outlines and intensely eosinophilic cytoplasm. The nuclei were often indistinct, the nucleoli did not stain well or were altogether absent, and occasionally cells appeared as mere shadows of a faint eosinophilic staining reaction and poorly defined outline without stainable nuclei. The

nuclear structures of the hippocampus, the pons, the medulla oblongata, and the dentate nucleus showed similar changes whereas the remainder of the cerebrum remained intact. The degenerative lesions corresponded closely to the pigmented areas seen macroscopically—a definite kernicterus.

It should be noted that this patient had one older brother who was in good health, and one other brother who was born jaundiced and died at the age of 8 months. Autopsy of this brother revealed a primary cirrhosis of the liver; it was not believed to be on the basis of erythroblastosis fetalis. Both parents of these infants were Rh positive. Microscopic sections of the lung and liver of the patient being studied were sent to Dr. Edith Potter at the University of Chicago. She reported that they did not show the changes usually associated with erythroblastosis fetalis. It should be noted that the clinical course was not typical of erythroblastosis fetalis—jaundice did not appear until the fourth day of life, there was no anemia present, and there were no young red cells in the blood. Pathologically, there were no extramedullary foci of hematopoiesis, but there was definite evidence of hemolysis in the liver which was full of heavy deposits of hemosiderin. In the present state of our knowledge it becomes necessary to report this as a case of kernicterus in a hemolytic jaundice of the newborn. It should be noted here that there is no pathologic picture characteristic of erythroblastosis fetalis as a disease entity, and it is my belief that when a clarification of terminology is established, when the Rh and other atypical agglutinins have been segregated and clarified, and when the pathologic findings have been standardized, it will result in the conclusion that erythroblastosis fetalis as a disease entity includes all of the endogenous acute hemolytic anemias of the newborn with or without erythroblastosis. This view and a suitable clarification of terminology have been presented by Madge Macklin.[13]

The eight remaining patients having kernicterus are still living. Five of these eight are included in the cases of erythroblastosis fetalis, four having the diagnostic Rh factors, the other patient not having the Rh factors tested.

This leaves three patients, jaundiced at birth, definitely not having erythroblastosis fetalis, and yet exhibiting some of the manifestations of kernicterus. One of these patients was premature with a birth weight of 4½ pounds, was cyanotic and kept in oxygen for ten days after birth. The second of these patients had a difficult breech delivery with evidence of birth injury. The third patient had rather marked evidence of cretinism and other deficiencies to account for his mental retardation and convulsions. Therefore these three patients should not be considered as cases of kernicterus, but rather as cases of birth trauma and cretinism complicated by some jaundice during the neonatal period.

An attempt was made to determine some correlation between the degree of jaundice and the severity of the manifestations of kernicterus. This was unsatisfactory chiefly because in about 50 per cent of the cases no icterus index was recorded and the degree of jaundice was estimated from the history in grades varying from 1 to 4 plus. It was observed that all those developing a kernicterus had at least 3 plus jaundice. In those that had icterus indices recorded all cases of kernicterus were over 100, yet the highest of 520 showed no neurological signs at the age of 11 months.

The ages of the patients observed clinically now range from newborn infants to children 6 years of age, and it has been noted during the period of observation that some patients who are spastic when jaundiced tend to improve as the jaundice subsides and as they grow older. Other instances have been reported in which the signs of spasticity or convulsions do not appear until months or even years after the jaundice has subsided. Certainly it is not possible to predict the mental development of a patient having kernicterus before he is 2 to 3 years of age.

SUMMARY

1. The literature pertaining to kernicterus and its relation to erythroblastosis fetalis is reviewed.

2. Twenty cases of erythroblastosis fetalis and fifteen cases of kernicterus were found in a study of thirty-four cases of jaundice of the newborn.

3. Twelve cases out of 20, or 55 per cent, of cases of erythroblastosis fetalis show some of the manifestations of kernicterus, a figure greater than that previously reported in the literature.

4. Thirteen of the twenty patients with erythroblastosis fetalis survived the neonatal period; of these thirteen, five have some of the manifestations of kernicterus, that is, 38 per cent of those who survive show some neurological sequelae.

5. This series confirms the practically universal association of kernicterus with hemolytic anemia of the newborn.

6. No cases of kernicterus are as yet reported as occurring solely with obstructive jaundice.

I wish to express appreciation to Dr. Douglas N. Buchanan for doing the neurological examinations.

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PERCUTANEOUS IMMUNIZATION AGAINST DIPHTHERIA

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CURRENT public health practice calls for the use of a stimulating dose of diphtheria toxoid in order to reinforce a declining immunity three years after primary immunization. As little as 0.1 to 0.2 c.c. of diphtheria toxoid, given subcutaneously or intracutaneously has been found highly effective as a secondary stimulus in the majority of cases, regardless of previous antitoxin levels.[1] Thus, one more injection has been added as a routine in the life of the young child, and at an age when the child's resentment is greater than in early infancy.

The realization that under certain circumstances the intact skin can react to antigens, as in the tuberculin patch test, led to an inquiry as to whether this route could be used for diphtheria toxoid. If comparable stimulation could be produced consistently by inunction of toxoid, it would greatly simplify the procedure.

From the Department of Health, City of New York.

Toxoid was supplied and the titration tests on the patients' blood were performed by the Lederle Laboratories, Inc., Pearl River, N. Y.

The literature contains several reports on the use of diphtheria toxoid percutaneously. In 1929, Loewenstein[2] used such a method in children who had not been immunized by subcutaneous injections of diphtheria toxoid. The material used was a formalinized whole culture broth of diphtheria bacilli concentrated from fifteen to twenty times, having the consistency of a salve. At two-week intervals three inunctions, each of 3 c.c. of this ointment, were carried out over large defatted skin surfaces until the substance had disappeared in the skin. No local nor constitutional reactions were encountered. In 68 per cent of the children so treated a positive Schick reaction was reversed six weeks after the last inunction. Antitoxin titrations were carried out in a smaller series of sixty-eight children who originally had been Schick-positive and then had received three inunctions of the toxoid concentrate. Seven of these children showed 1 unit; 3 children, ½ unit; 5 children, more than ⅕ unit; the rest, between ⅕ and $\frac{1}{30}$ unit of diphtheria antitoxin per cubic centimeter of serum.

Subsequent reports showed considerable variation. Urbanitzky[6] found that percutaneous immunization produced reversal of the Schick test in 100 per cent of twenty-four children up to 2 years, in 87.5 per cent of twelve children between 2 and 3 years, and in 81.3 per cent of thirty-four children between 3 and 6 years of age. Four Schick tests were done on each patient, one before and one two months after each of three inunctions. On the other hand, Zikowsky[8] reported fifteen cases of diphtheria in children "immunized" with Loewenstein's ointment from forty-five days to nine months prior to the disease. In 1934, Siegl and Drach[5] reported a series of 222 children who were treated with three inunctions of 3 c.c. each of the salve and received a Schick test from six to eight weeks after the last treatment. In ninety-seven children the test became negative, and in 125 it remained positive, that is, the ointment was effective in 43.7 per cent of the cases. Nobel[3] was even less successful in his study on 206 Schick-positive children who received three inunctions, and a second Schick test twenty-two days after the last treatment. One hundred thirty-two children, or 65 per cent, remained Schick-positive; seventy-four children, or 35 per cent, became Schick-negative. The Schick test was repeated in 171 of these 206 children five months after the last inunction, with the same result: only 35 per cent of the children were Schick-negative.

These discrepancies were ascribed by the various investigators to differences in the immunizing quality of the Loewenstein ointment or to differences in the standards of the Schick toxin used for testing. In the light of our present knowledge additional factors aid to explain the different results. The Schick test itself has been shown to have a not inconsiderable antigenic action,[4] a factor which undoubtedly contributed to the results. Furthermore, diphtheria was not a rare disease in Vienna between 1929 and 1934; natural immunizing processes may have had some influence. Unfortunately none of the reports is supported by an adequate series of controls.

MATERIAL AND METHODS

Through the cooperation of Mrs. Marjorie Middleton, Director, a series of children were studied at the Winifred Wheeler Day Nursery. In this institution, children, largely of working mothers, are under care from 8 A.M. to 5 P.M. All the children had received primary immunization from two to five years previously. Alternate cases were selected for the treated and control series but in some instances children dropped out of the school and insufficient data were accumulated to include them in the analysis.

At the first visit a specimen of blood was withdrawn and inunction with toxoid or control material performed. This procedure was repeated two weeks later. Two to four months later, a third specimen was obtained. No Schick tests were done at any time. After defatting with acetone, inunctions were carried out over the whole arm until the material disappeared which usually required one to two minutes of rubbing.

Treated Series.—The inunction material contained diphtheria toxoid prepared from veal infusion broth with peptone, concentrated ten times by ultra filtration to 320 Lf.* and preserved with merthiolate 1 to 10,000. The toxoid was mixed with an equal volume of an emulsion base consisting of 88 parts mineral oil, 8 parts oleic acid and 4 parts triethanolamine. After shaking, this mixture made a white emulsion which readily disappeared when rubbed on the skin. One cubic centimeter of this emulsion therefore contained 160 Lf; ½ c.c. which was used for the inunctions in this study contained 80 Lf. A stability test done on the material after one month of incubation at 37° C. showed no loss of potency. This material was used in fourteen cases.

In four cases another vehicle, called Percutanol No. 1† was used. Three parts of the same concentrated toxoid were mixed with one part of the vehicle. The mixture resulted in a clear solution which disappeared even more readily when rubbed on the skin. One-third of a cubic centimeter of this mixture, equaling 80 Lf, was used.

Control Series.—Children were anointed in exactly the same fashion as the experimental group with the same emulsion base but minus the toxoid. Blood specimens were also obtained at the same intervals.

Measurement of Antitoxin.—Serum titrations were carried out in duplicate using the guinea pig skin test.[1]

RESULTS

In the final analysis there were eighteen cases in the treated group and fifteen controls. No untoward reactions, either local or general, were observed. The results are shown graphically in Chart 1. The logarithm of the initial titer is plotted against the logarithm of the higher of the two subsequent titers. The diagonal line indicates the position of no change, that is when the final titer equaled the initial titer. To the left of this line are the cases in which the titer fell and to the right are those in which the titer rose.

It is evident from inspection that while there are differences between the two groups they are not of a very high order. No case in the control group showed an increase of more than two titration steps while four of the treated group showed an increase of three or more. In three of these instances the original titer was the lowest measured, $\frac{1}{2000}$ u. of antitoxin.

It seems safe to conclude that while a percutaneous route can produce some increase in antitoxin titer, it is not sufficiently consistent to be of practical use. One may explain this inconsistency in part on the basis of variation in character of the skin, but, at present, no obvious way to compensate for such variation is apparent. It is, of course, possible that either larger doses of toxoid‡ or a more effective vehicle might produce better results.

*Flocculation units.

†Supplied by the Wallace Laboratories, New Brunswick, N. J.

‡In cooperation with Dr. Arthur Goldfarb of the Lincoln Hospital, New York, one of us (V.) applied up to 640 Lf of diphtheria toxoid percutaneously by various methods of nineteen children who had been immunized more than three years previously. Eleven returned for the final blood examination. In only three of these eleven children were the antitoxin titers increased as much as ten times the previous level. From these few experiments it appears that larger doses of toxoid do not promise substantially better results.

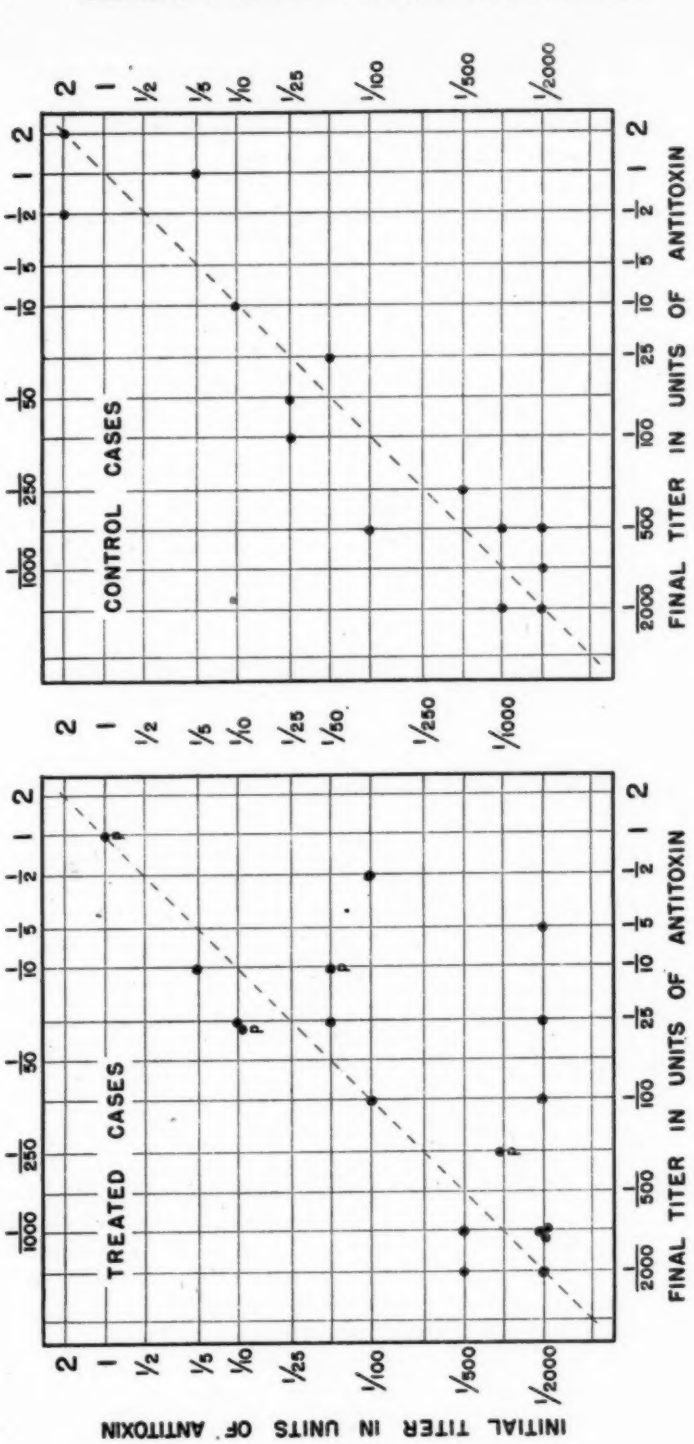

Fig. 1.—Effect of percutaneous inunction of diphtheria toxoid on antitoxin titer of previously immunized children.

The considerable change between the two readings in the control group is a point of interest. Only three of the fifteen cases showed the same final titer as the original one, and six showed variations as great as two titration steps. Although this variation may be a true expression of change in antitoxin content of the blood, it is more likely an indication of the range of accuracy of the titration test itself.

The discrepancy between the results here presented and those in the literature serves to emphasize again the danger of using reversal of a Schick test as a measure of change in antitoxin titer, since the test itself has sufficient potency as an antigen to affect the results.

SUMMARY AND CONCLUSIONS

1. In a series of children previously immunized against diphtheria, stimulating doses of concentrated diphtheria toxoid were given by percutaneous inunction.

2. While there were differences between the treated and control groups, they were not of a high order.

3. Evidence of stimulation of antitoxin response was evident in less than 25 per cent of the treated group.

4. With the method used, percutaneous administration of booster doses of toxoid is not a practical procedure.

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GALACTOSEMIA WITH HEPATIC DAMAGE

REPORT OF A CASE IN AN INFANT WITH RECOVERY

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IN 1917 Göppert[1] reported the case of a child with galactosuria and hepatomegaly. First seen at the age of 2 years, 5 months, the patient was markedly stunted and undernourished but improved strikingly when placed on a lactose-free diet. The liver became much smaller. Two siblings had had jaundice and hepatomegaly at or soon after birth and had died at 6 and 4 weeks of age. Another, who survived, had slight icterus and hepatomegaly. Göppert, therefore, reported his case as one of a congenital and familial disorder.

Holt and McIntosh[2] briefly mentioned another case associated with malformation of the liver, but the first comprehensive analysis of the disorder was made by Mason and Turner in 1935.[3] Their patient, an infant, had galactosuria and liver disease, both of which disappeared on a lactose-free diet.

From the Department of Pediatrics Stanford University School of Medicine

In 1943 Norman and Fashena described a similar case.[4] So far as we know ours is the only other proved case of chronic galactosemia with secondary liver disease.

It is well known that, of the three common monosaccharides, glucose and fructose are more readily converted into glycogen than is galactose,[5] a fact which forms the basis of the galactose tolerance test. Rare individuals, however, are so deficient in the ability to metabolize galactose that they develop chronic galactosemia, which causes galactosuria, the renal tubules being unable to reabsorb galactose. This condition may be associated with a type of liver failure that is rapidly and apparently completely cured when galactose is removed from the diet. The following is a case in point.

CASE HISTORY

J. J., a white American boy born March 30, 1944, was first admitted to the Pediatrics Service of Stanford University Hospital on April 24, 1944, for abscesses in the right groin.

A. *B.*

Fig. 1.—*A*, J. J. before therapy. Note ascites, engorgement of abdominal veins, and scrotal edema.

B, J. J. after twenty-eight days of therapy. Ascites, engorgement of abdominal vessels and scrotal edema have disappeared.

Pregnancy and labor were uneventful. He weighed 9 pounds at birth but had steadily lost weight to 7 pounds, 9 ounces. At 5 days of age he developed a moderate jaundice, which cleared in two weeks. Since birth he had nursed poorly and vomited frequently despite variations in diet including breast milk and formulas of several acceptable varieties.

A week before entry, hot, purplish lumps had appeared in the right groin. They were incised, and pus was drained, but a new abscess had formed. There had been only slight fever.

The family history was noncontributory. There were no siblings.

Physical examination, negative in other respects, showed a protuberant abdomen without fluid wave; a moderately hard liver whose edge was at the level of the umbilicus; emaciation in the extremities; and a red, hot swelling in the right groin.

Following are the laboratory data: The blood count showed 4.0 million red blood cells; 75 per cent hemoglobin (Sahli); 16,000 white blood cells, of which 56 per cent were neutrophiles. The urine revealed a 3 plus reaction for sugar (Benedict's test); no acetone; and albumin 2 plus. The blood sugar, three hours after feeding, was 200 mg. per cent. Culture of serous material from the right groin grew a coagulase positive *Staphylococcus aureus*.

Eight days of sulfadiazine therapy, following incision of the abscess, led to complete disappearance of the infection and a weight gain to 8 pounds, 4 ounces. In the meantime it was discovered that the urinary sugar was not fermented by yeast. It was assumed that the baby had lactosuria, and he was sent home May 4 on a formula of powdered milk.

A few days later the infant's scrotum and feet began to swell, and his abdomen became greatly distended. He re-entered the hospital on June 1, at the age of 2 months. His appearance then was strongly suggestive of hepatic cirrhosis. The skin over the abdomen was tight and shiny, and the superficial veins were engorged, as in typical portal obstruction. The liver reached the umbilical level, and there was pitting edema from feet to knees. The weight was 10 pounds.

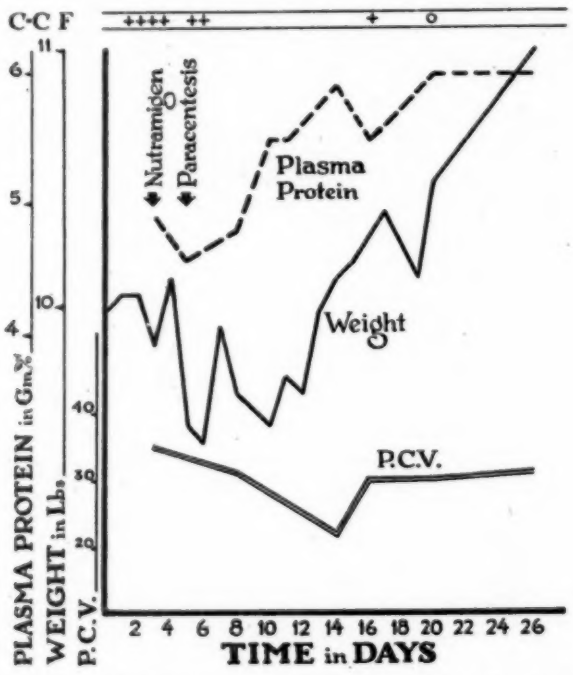

Fig. 2.—Chart showing changes in plasma protein, packed cell volume, and gain in weight following lactose free diet.
C-C F = cephalin cholesterol flocculation.
P.C.V. = packed cell volume.

Following are the laboratory data: Examination of the blood showed 3.06 million red blood cells; hemoglobin 56 per cent (Sahli); white blood cells 15,850; packed cell volume 35 per cent. Fasting blood sugar was 180 mg. per cent; plasma protein, 4.8 Gm. per cent; icterus index, 10; cephalin flocculation test, 4 plus. Examination of the urine showed sugar 3 plus (Benedict); albumin 2 plus (sulfosalicylic acid). The Addis count was as follows: 175 c.c. per 16 hours; specific gravity, 1.023; pH 6.0; protein, 0.544 Gm.; casts, 100,000, all granular; leucocytes and epithelial cells, 2 million; red blood cells, 1 million.

Tests for identification of the urinary sugar gave the following results: (1) There was no fermentation with yeast after incubation at 24° C. for fourteen hours; this ruled out

glucose and maltose. (2) Rubner's test gave a yellow reaction; this ruled out lactose, glucose, and fructose. (3) Bial's orcinol test for pentose was negative. (4) The mucic acid test with nitric acid produced crystals characteristic of either lactose or galactose. (5) Barfoed's test for monosaccharides was negative; this test, in the light of the positive Benedict's test, the negative tests for disaccharides, and the positive mucic acid test, can probably be disregarded, especially since Hawk[6] states that it is unreliable for urine. The positive mucic acid test taken in conjunction with the negative Rubner's test for lactose therefore appears to identify the nonfermentable urinary sugar as galactose.

A diagnosis of galactosemia with marked impairment of hepatic function was made, and the diet accordingly changed to one containing no lactose. This consisted of Nutramigen* which contains casein hydrolysate, dextrimaltose, Brewer's yeast, and calcium, potassium, and magnesium salts. The baby was also given ascorbic acid, percomorph oil, and ferrous sulfate.

Twenty-four hours after this regimen was started the urine still showed a 2 plus reaction for sugar and protein excretion at the rate of 0.544 Gm. per twenty-four hours, but in forty-eight hours it was free of sugar, and the protein was 0.272 Gm. per twenty-four hours. At this time the fasting blood sugar was 75 mg. per cent, and the icterus index was 5.

Although the baby took the formula well, he continued to vomit. The abdomen was still distended. Paracentesis yielded 480 c.c. of cloudy yellow fluid with a specific gravity of 1.006. Vomiting became very infrequent. Without other treatment institution of the lactose-free diet was followed by dramatic improvement. After ten days, the ascites, edema, and distention of the abdominal veins had entirely disappeared; the plasma proteins had risen to 5.8 Gm. per cent; the protein had disappeared from the urine, and the baby was gaining weight without any signs of abnormal water-retention.

On the thirteenth day the cephalin flocculation test was only 1 plus, and on the seventeenth day it had become negative. As the plasma proteins rose, the packed cell volume fell to 22 per cent on the tenth day, revealing the true depth of the anemia, but by the twenty-first day had reached 31 per cent. At that time the blood showed 2.92 million red blood cells and 60 per cent hemoglobin. The liver diminished in size, but on the thirtieth day of treatment was still 3 c.c. below the costal margin. On June 10, 5 days after the urine had become free of sugar, 10 Gm. of lactose were given in the formula. Seven hours later the urine contained traces of sugar, but at twenty-four hours was again sugar free.

The lactose-free diet has been continued. When last seen at the age of 7 months the baby weighed 17 pounds, 11 ounces, and appeared entirely normal and healthy, except for slight enlargement of the liver. There was no trace of edema. The packed cell volume was 42 per cent, and the plasma proteins 6.4 Gm. per cent. The urine contained neither sugar nor albumin.

DISCUSSION

Galactosemia is clearly a metabolic anomaly in which the liver is unable to convert galactose to glucose, at least not at the normal rate. This situation results in galactosuria, impairment of hepatic function, and such later sequelae as malnutrition and dwarfing. The syndrome poses certain questions on the mechanism of its production. On the basis of their observations, which were confirmed by Norman and Fashena, Mason and Turner suggested the following theory: Since the body cannot metabolize galactose, this sugar accumulates in the blood and causes a depression of blood glucose. The high blood galactose level "deceives" the regulators of blood sugar and causes an excessive conversion of glucose to glycogen, which causes hepatomegaly and hepatic dysfunction. When lactose, the source of galactose, is withdrawn from the diet, normal glycogen-glucose equilibrium is re-established and the liver returns to normal. The low level of blood glucose results in tissue damage, presumably to the liver and kidney.

Three things make us question the validity of this theory: First, there is surprisingly little liver disturbance in glycogen-storage disease, in which excessive and extreme storage of glycogen in the liver is known to occur. Second,

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ordinarily the deposition of glycogen in the liver tends to protect the liver. Third, hypoglycemia from other causes appears not to damage the liver or kidneys.

The presence, in our case at least, of a strongly positive cephalin flocculation test nevertheless demonstrates the presence of degenerative changes in the liver. We suggest as another hypothesis that galactose itself (possibly as a polymer) is stored in the liver, is directly injurious to it, and is responsible for hepatic injury.

The proteinuria might be due to renal damage by galactose. It is interesting, however, that in our case the proteinuria was accompanied by an otherwise normal Addis count and by a normal serum creatinine level. This suggests the possibility that there was no renal lesion at all, and that the proteinuria was due to the production of abnormal plasma proteins which were excreted by the kidneys.

Evidence that ingested galactose may not be excreted quantitatively in the urine is found in our observation that after ingestion of 7 Gm. of lactose (containing 3.5 Gm. of galactose) only traces of sugar were found briefly in the urine. This can mean either that a certain amount of galactose was actually converted to glucose in the liver, or that it was stored there, or both. Our hypothesis, like that of Mason and Turner, can be proved only by analysis of liver tissue, which has not as yet been done.

SUMMARY

The four previously described cases of galactosemia with hepatic damage are briefly reviewed. A fifth case is presented with studies of liver and kidney function before and after therapy. A new hypothesis is suggested to explain the liver damage: The inability of the body to metabolize galactose causes the latter, or its polymer, to be stored in the liver and results in hepatic dysfunction. The process is reversed when galactose is eliminated from the diet. The proteinuria may be due to a similar process in the kidney or to the production of an abnormal plasma protein.

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RHEUMATIC HEART DISEASE WITH ASSOCIATED MENINGOENCEPHALITIS

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RHEUMATIC infection affects not only the heart and joints, but also the lungs, pleura, kidneys, and other tissues in its generalized involvement of the fibrous tissues and the vascular bed. Clinical disturbances, however, of the central nervous system, with the exception of Sydenham's chorea, are rare in rheumatic fever. Characteristic pathologic changes have not been recorded for chorea and only rarely have lesions suggestive of rheumatic fever been observed in association with other disturbances of the central nervous system.

Recently we have observed the clinical manifestations of meningitis in a child with chronic rheumatic carditis. The post-mortem findings revealed no changes in the central nervous system other than ones similar to the rheumatic type of perivascular lesions which were widely distributed in the heart and lungs.

Bruetsch[1-4] has repeatedly pointed out that many psychotic patients with post-mortem evidence of old rheumatic heart disease have widespread rheumatic endarteritic changes in the vessels of the meninges and subcortex. In fact, he has described such changes in 9 per cent of patients with dementia praecox. Similar observations have been reported by Kernohan, Waltman and Barnes[5] who described swelling of the endothelial cells, thrombi in situ, and tiny emboli in the cerebral vessels in twenty-five out of twenty-six psychotic patients with rheumatic endocarditis.

Other lesions of the nervous system have also been described in acute rheumatic infections. Thus acute hemorrhagic encephalitis has been observed by Winkelman and Eckel,[6] by Alpers,[7] and by Dobbs and de Saram.[8] The first authors stated that the changes were similar to those produced by toxemia and acute infection. Alpers presented a series of cases in which, regardless of the primary disease, similar hemorrhagic changes were found in the brain. Case 2 in his series was one of acute rheumatic carditis with terminal pneumonia, in which the lesions in the nervous system were similar to those found in the other nonrheumatic cases of the series. The lesions involved the small cerebral vessels whose swollen endothelium was surrounded by perivascular foci of cells, some of which showed necrotic centers. Dobbs and de Saram presented a case of acute rheumatic carditis with typical joint manifestations in a child 8 years of age, who terminally had hyperthermia after developing encephalitic symptoms. The brain showed hemorrhagic encephalitis. Frisch[9] described a child with typical acute rheumatic fever who, after developing diffuse encephalitic symptoms, recovered completely. Cerebrospinal fluid, obtained at the peak of the clinical disturbance, showed only a moderate increase of leucocytes (70 per cubic millimeter) and a slight increase in globulin. The clinical history reported by Bourne[10] is somewhat similar to the one observed by us. His patient had typical acute rheumatic arthritis, carditis, and a pericardial effusion. Seventeen days after the onset of the attack, the patient developed signs of severe meningeal irritation. The cerebrospinal fluid was

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sterile. Its glucose and chloride content was normal, but the protein and white cells were slightly increased. Bourne believed that this patient, who finally recovered, had a rheumatic inflammation of the meninges.

CASE REPORT

F. B., a Negro boy 12 years of age, was admitted to the pediatric ward at Temple University Hospital on March 9, 1944. Within the previous twenty-four hours he had developed severe headache, vomiting, pain in the neck and back, and drowsiness which gradually increased to a semicomatose state.

Between the ages of 4 and 8 years he had German measles, chicken pox, measles, and whooping cough. At the age of 5 years he developed rheumatic fever. A systolic apical murmur could be heard thereafter. He was observed by his family physician at regular intervals, and his physical activity had been limited from the onset of his first attack. In January, 1944, he became ill, complaining of weakness, malaise, and occasional headaches. At this time he was found to have moderate hypertension. The systolic pressure ranged from 135 to 145 mm. mercury. He was thought to be in cardiac decompensation and was treated with digitalis and sedatives. He was kept at strict bed rest. Three weeks before admission to the hospital he complained of severe headache and was disoriented. These symptoms disappeared within twelve hours and he was gradually improving until there was a sudden exacerbation just prior to his admission to the hospital.

Physical examination revealed an acutely ill, underweight 12-year-old Negro male who was disoriented and negativistic. His temperature was 99° F.; pulse, 96; respirations, 20; blood pressure, 100/60. Fundal examination revealed a pale disk but no choking. A mucopurulent discharge was present in his nose. His mouth showed evidence of moderate dehydration. The lungs were normal by physical examination. His heart was enlarged to the left and downward by percussion. Systolic and diastolic murmurs were heard at the apex and over the precordium. There was radiation of the systolic murmur toward the axilla. No petechiae were found in the skin or mucous membranes. The neurologic examination revealed marked nuchal rigidity and bilateral Kernig's signs. Motor power and sensation were grossly normal.

The cerebrospinal fluid was purulent; the pressure could not be recorded because the patient struggled constantly. On the basis of the history, physical findings, and the purulent spinal fluid a diagnosis of purulent meningitis was made. Two grams of sodium sulfadiazine in 100 c.c. of physiologic saline solution were administered intravenously and sulfadiazine was then continued by mouth in doses equivalent to 0.1 Gm. per kilogram of body weight per day. In eight hours he was much improved although he was still drowsy and still had signs of meningeal irritation. Lumbar puncture was repeated at this time and again yielded purulent fluid. The pressure was 13 mm. of mercury. The day after admission he was alert, oriented, and had only moderate nuchal rigidity. On March 11 (two days after admission) another lumbar puncture was performed in order to obtain more fluid for culture. At this time the fluid was xanthochromic and under 18 mm. pressure.

During the next few days all signs of meningeal irritation disappeared, the temperature remained normal and he developed no new findings except a moderate leucopenia. No organisms were isolated from the blood culture taken before sulfadiazine was administered or from six cultures of the spinal fluid.

On March 21 (twelve days after admission) he seemed quite well but for the first time complained of severe frontal headache. A lumbar puncture was again performed. This time the pressure was 10 mm. of mercury and the fluid clear and colorless. His headache was somewhat relieved by this procedure, but recurred the next day and the spinal puncture was repeated. The pressure was 10 mm. of mercury and the fluid clear and colorless. During the next twenty-four hours he constantly complained of headache but had no abnormal signs. On March 23 (fourteen days after admission) he refused breakfast and ten minutes later was found dead. At no time during his hospital course did his rectal temperature reach 100° F., nor did his pulse exceed 100.

The laboratory data are given in Table I.

NECROPSY FINDINGS

Autopsy was performed two hours post mortem.

The heart was enlarged; it weighed 200 grams after removal of the blood. The average weight of the normal heart at this age is 125 grams. The enlargement was due to hyper-

TABLE I. LABORATORY DATA

DATE	W.B.C.	POLYMORPHONUCLEARS (%)	CULTURE	CHLORIDE (MG.)	SUGAR (MG.)	PROTEIN (MG.)	COLLOIDAL GOLD CURVE	TRYPTOPHANE	LEVINSON
			SPINAL FLUID FINDINGS						
3/9	2,800	–	Sterile	640	53	206	–	–	–
3/9	2,400	90	Sterile	676	37	206	4555555553	Negative	Positive
3/11	1,000	60	Diphtheroids (Contaminant)	664	44	Moderate increase	5555554321	Positive	Positive
3/20	–	–	Sterile	680	49	187	–	–	–
3/21	244	85	Sterile	680	49	Slight increase	–	–	–
3/22	–	–	Sterile	704	53	120	5555420000	–	–
3/23	Post-mortem culture from meninges was sterile								

BLOOD COUNTS							
Date	3/9	3/13	3/15	3/17	3/18	3/20	3/22
Hemoglobin	12.0	11.0	10.5	10.0	10.0	10.0	10.5
R.B.C.	4.4	4.4	3.7	4.2	4.5	3.9	3.7
W.B.C.	21,800	3,800	3,300	3,700	6,800	4,800	6,300

Urinalyses; five urinalyses were negative with the exception of that done on 3/9 which showed a trace of albumin and about 40 R.B.C./H.P.F.

Serology; Kolmer, Kahn, and Mazzini reactions were all negative.

Tuberculin tests; purified protein derivative No. 1 and ½ strength purified protein derivative No. 2 were negative.

Blood culture taken on 3/9 before the administration of sulfadiazine was sterile.

Nasopharyngeal culture on 3/9 showed pneumococci types 3, 13, 23, and 28 and nonhemolytic Staphylococcus aureus.

Plasma CO_2 on 3/9 was 54 volumes per cent.

Sulfadiazine levels ranged from 2.6 to 8.2 mg. per cent.

Roentgenologic findings: Posteroanterior and lateral chest films taken on 3/13 were negative for pulmonary disease. The heart shadow was of normal size and configuration.

Skull films taken on 3/15 were normal except for minimal sclerosis of the mastoid cells.

trophy of the left ventricle characteristic of that seen in hypertension and to dilatation of all four cavities. The leaflets and chordae tendinae of the mitral valve were thickened. Along the edges of closure there was a row of verrucous nodules characteristic of active rheumatic inflammation. There was a poorly defined roughened patch in the endocardium of the posterior wall of the left atrium. The epicardium had lost its normal sheen but there was no grossly demonstrable exudate. Examination of numerous sections of the valve leaflets, myocardium, and epicardium revealed degenerative and inflammatory changes characteristic of active rheumatic carditis. (Fig. 1.) The process was minimal but definite in the epicardium.

The lungs were slightly heavier than normal owing apparently to a mild congestion. The microscopic sections (Fig. 2) revealed vascular lesions similar to those described by Goûley and Eiman[11] and by Epstein and Greenspan[12] as characteristic of rheumatic infection. Adhesions were present over a small area on the lateral aspect of the right lower lobe. The spleen was moderately enlarged and the follicles abnormally prominent.

The mesenteric nodes were enlarged. Microscopic study revealed a mild inflammatory hyperplasia. The kidneys were quite congested. The vessels showed none of the changes which characterize hypertension.

The brain was pale, dry, and sticky. The convolutions were markedly flattened. The calvarium was unusually thin suggesting increased intracranial pressure over a considerable period of time. The tentorium bulged upward and the subtentorial cerebrospinal fluid was found to be under considerable pressure. This increase in pressure was further manifested by a pronounced herniation of the cerebellum through the foramen magnum. Gross examination of the sectioned brain failed to reveal evidence of inflammation. The meninges were carefully examined for gross evidence of suppuration and tubercles. None was found. The inner ears and the mastoids were normal. The venous drainage channels were all normal.

When sections of the brain, choroid plexus, and meninges were examined microscopically a rather unusual inflammatory reaction was found. There was a lymphocytic infiltration about most of the small vessels of the gray and white matter. In some areas, large cells closely resembling those characteristically seen in the Aschoff body were intermingled with the lymphocytes (Fig. 3). The resulting morphology and pattern of these aggregates could hardly be said to be identical with the Aschoff body but many of them contained very similar elements. The reaction in the meninges and choroid plexus was almost entirely lymphocytic (Fig. 4).

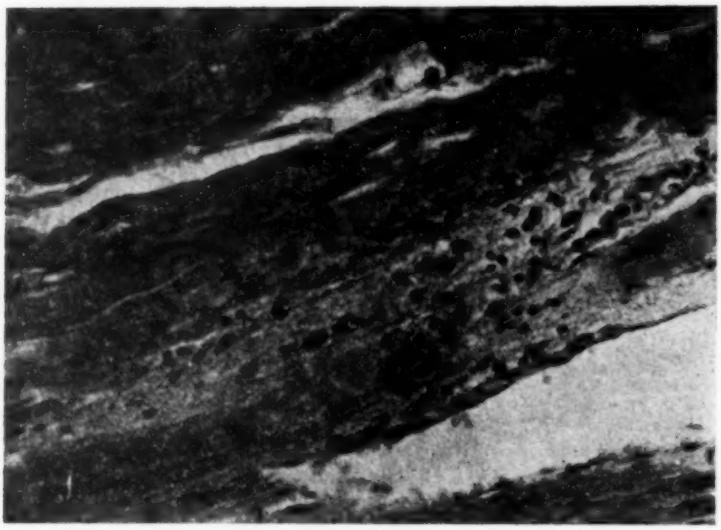

Fig. 1.—Heart. The collagen shows hyalinization and necrosis. There are several large cells characteristic of those seen in the Aschoff body. The other inflammatory cells are lymphocytes.

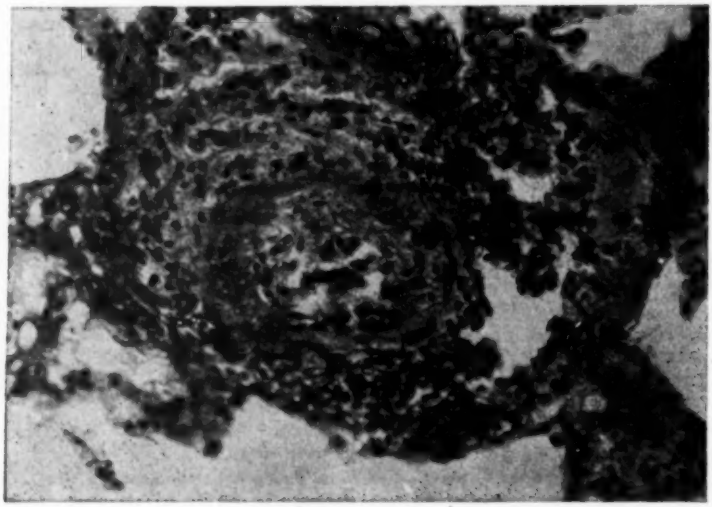

Fig. 2.—Lung. A small pulmonary vessel showing the changes described in active rheumatic fever. The intima and subintima are damaged. The vessel wall is hyalinized. The surrounding exudate contains Aschoff cells, lymphocytes, and eosinophiles.

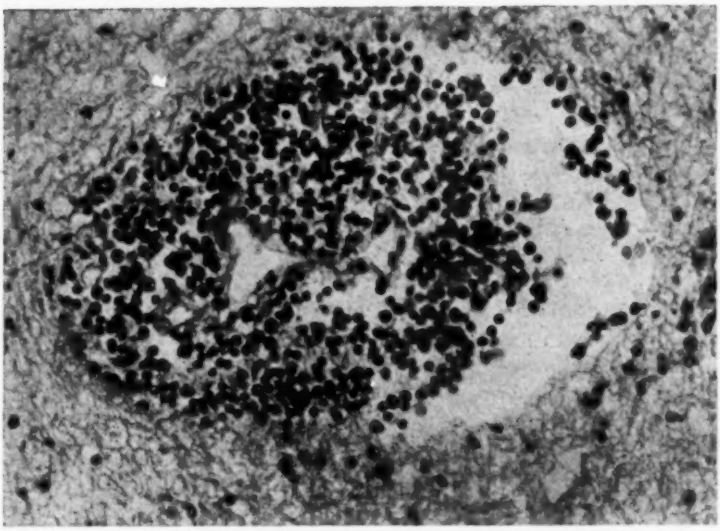

Fig. 3.—Brain. An aggregation of inflammatory cells in the brain. Centrally there are large cells of the Aschoff type. The smaller cells are lymphocytes.

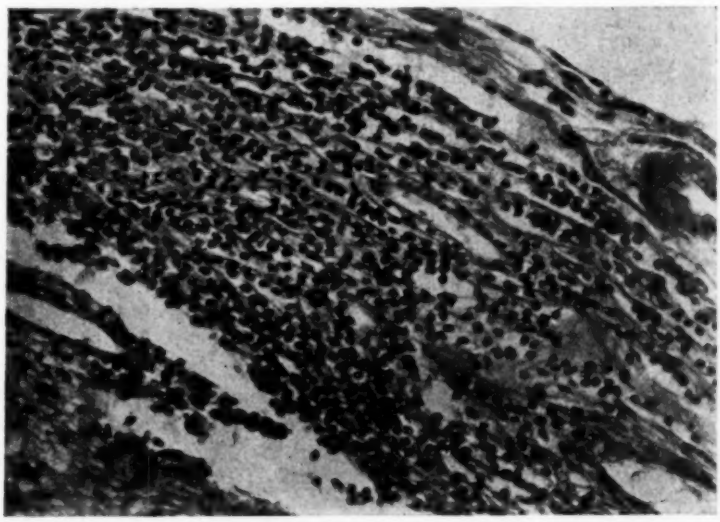

Fig. 4.—Meninges. The meninges are thickened by an infiltration with lymphocytes. The large cells which characterize the perivascular lesions of the brain, lung, and heart are not found.

DISCUSSION

Numerous writers have described the extracardiac, vascular lesions which occur in the active stage of rheumatic fever. The lesions in the lungs were described by Gouley and Eiman[11] and by Epstein and Greenspan.[12] We are inclined to the belief that the inflammatory reaction seen in the meninges, brain, and cord tissues of our patient was of rheumatic origin. While the appearance of the cellular aggregation is not that of the Aschoff body, the cellular components are similar if not identical. The clinical and post-mortem evidence for an active rheumatic carditis seems irrefutable. The lesions in the lung are consistent with those described in rheumatic fever. Thus it seems warranted to assume that the cerebral and meningeal lesions were produced by the same etiologic agent.

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MYOSITIS OSSIFICANS PROGRESSIVA

A REVIEW OF THE LITERATURE WITH REPORT OF A CASE

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MYOSITIS ossificans progressiva is a peculiar disease of the locomotor system in the growth period of children, affecting not only the muscles but tendons, ligaments, fasciae, and aponeuroses, characterized by the appearance in them of masses of bone or areas of calcification. It has periods of exacerbation and regression and is commonly associated with various congenital anomalies, the commonest being malformation of the great toes.[1] The disease is quite rare and seems to occur mainly in the Anglo-Saxon race; only about 160 cases have been reported in the literature, the first being described in 1692.[2] It occurs more commonly in males, in a ratio of 4:1.

ETIOLOGY

There are many theories as to the cause of myositis ossificans progressiva. Some authors report the disease occurring regularly in some families, and to be hereditary in nature. Others believe that infection, particularly the rheumatic type, plays a prominent role. There are many family histories of rheumatic fever and rheumatic heart disease. Trauma is many times listed as the

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original offender but is supposed to be only a starting point in susceptible individuals. Central nervous system lesions, such as epilepsy and transverse lesions of the spinal cord, are occasionally associated. However, it appears that all of the above-mentioned conditions seem to predispose in the production of the disease.[3]

CLINICAL FEATURES

The disease may start following an injury or infection of some type, and the parents may notice the appearance of small, soft, cystlike masses over different parts of the body. These lesions have a tendency to break down and drain; whole muscle areas may calcify and form bone. At other times, the disease may be ushered in by a true rheumatic infection with pyrexia and swelling of the joints, the masses in the muscles appearing later. In general, the disease affects the dorsal aspect of the trunk, but never affects the tongue, heart, larynx, diaphragm, or sphincters. Many studies have been made on blood and urine chemistry, but none have been particularly significant; calcium, phosphorus, creatine and creatinine reports have all been negative. One study has been of importance in that a biopsy revealed a high phosphatase content and led the authors to believe that connective tissue proliferation was the primary factor.[4] In 75 per cent of the cases, there is an associated congenital anomaly. The deformity may be of several different types—there may be microdactylia of the great toe with an ankylosis of the inner phalangeal joint; there may be an ankylosis of the metatarsal phalangeal joint with the absence of one phalanx. Similar changes may occur in the thumb; occasionally a double congenital hallux valgus occurs.

PATHOLOGY

Grossly, one finds in the later stages of the disease, a continuous band of bone from the occiput to the pelvis. There are also many loose masses of bone in all areas. The articular cartilage of the joints is not affected, only the capsule, with a resulting complete ankylosis. Microscopically, the primary lesion consists of a replacement of the inner fibrillary connective tissue network of the striated muscle by a young, embryonic connective tissue network. This organizes into firm, fibrous tissue which retracts and presses on the muscle fibers which then atrophy, lose their transverse striations, and the longitudinal markings become more prominent. The nuclei may or may not multiply, but if they do, there is then a formation of a giant cell system in many places. Cartilage cells then attach themselves to osseous bands, and osseous trabeculae form. Because of the variation in stage of the pathological process, the microscopic picture varies considerably.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of myositis ossificans progressiva is made by a history of rheumatism, injury, or the appearance of cystlike masses in different areas over the body. X-ray reveals calcium deposits plus true bone formation. The bones will suffer from decalcification with osteoporosis of the whole skeleton; they may even fracture. Differential diagnosis includes myositis fibrosa, dermatomyositis, polymyositis hemorrhagica, multiple exostosis, Pott's disease, and calcinosis interstitialis ossificans. The most important point in the differential diagnosis is the fact that in myositis ossificans progressiva, there is actual bone formation. No bone formation occurs in the other diseases except in multiple exostosis. In this condition all bone is attached to the bony skeleton.

TREATMENT AND PROGNOSIS

There is no specific treatment. Many things have been tried, but none of them has been particularly successful. Beryllium carbonate—to lower the phosphorus and thus prevent calcification—failed to be effective; ketogenic and low calcium diets, x-ray, parathyroid, vitamins, disodium hydrogen phosphate, and surgical removal of the bones have all failed.[5] The prognosis is grave. If the disease comes on in infancy, the children seldom live to be over 15 years old. Puberty always presents a difficulty, and there has never been a report of a cured case of myositis ossificans progressiva after its onset. Since the disease has exacerbations and remissions, there are several enthusiastic reports in literature. As the disease progresses, there is involvement of the muscles of respiration with a resulting limitation of thoracic movement. Pneumonia and tuberculosis sometimes intervene.

Fig. 1.—Left posterior thigh with bone formation. This area previously drained white chalky material.

CASE REPORT

C. R., male, aged 8 years. Onset of illness in November, 1941, with temperature of 101° F., associated with swollen and painful joints. A diagnosis of rheumatic fever was made at that time, and the patient treated with bed rest and aspirin. An abscessed tooth was removed, and he seemed to improve. The child's joints became more stiff; he lost 11 pounds in weight over a period of a few months. Anorexia was a prominent symptom. The family history was negative; birth and development were normal. Previous illnesses included a streptococcus throat at 3 years of age.

Examination in May, 1942, revealed an undernourished child who appeared chronically ill. Tonsils were red and moderate in size. On walking, the child bent forward in a fixed position with a stiff spine, and was quite unsteady. There were atrophic changes in

all muscles, and the fingers were fusiform (sweet potato joints). All other joints revealed limitation of motion and were quite painful with moderate swelling.

Laboratory Examination.—Hemoglobin, 65 per cent; white cell count 6,250; 71 per cent neutrophiles; 17 per cent lymphocytes; 1 per cent eosinophiles; and 11 per cent monocytes. The urine was normal; blood culture, negative. The basal metabolic rate was +10. The first blood culture revealed *Staphylococcus aureus*, hemolytic type, and one repeated ten days later was negative. X-ray of the teeth showed no infection. Sedimentation rate, 30 mm. per hour (corrected Wintrobe).

The child's temperature while he was in the hospital varied from 99 to 101.6° F. A diagnosis of atrophic arthritis was made, and general symptomatic treatment followed. A tonsillectomy was advised, but because of persistent gingivitis, it was decided to send the child home for dental care and that he return and have the tonsillectomy later. During the interval at home, the gingivitis disappeared.

Fig. 2.—X-ray of lower extremity reveals osseus change in muscles.

The patient was next seen in December, 1943. At that time his gums had cleared up and his tonsils appeared the same. On his left axilla there was a cystlike tumor about 4 cm. in width and 3 cm. in length which was not attached to the bone. Also present was a large, indurated area with ecchymosis and redness on the posterior aspect of the thigh; this was quite tender. (Fig. 1.) X-rays were obtained; the diagnosis of myositis ossificans progressiva was made, and he was admitted to the hospital. (Figs. 2 and 3.) The child was more stooped at this time, and all joints were becoming more fixed. The tuberculin and Wassermann tests were negative; hemoglobin, 65 per cent; red blood cells, 3,810,000, with normal white count. Corrected Wintrobe, 34. Urine was normal. Blood serum calcium, 11.5; blood serum phosphorus, 4.9; blood serum phosphatase, 8.1 Bodansky units; blood creatinine, 0.858 mg. per cent; creatine, 2.43; plasma cholesterol, 1.34 mg. per cent; plasma total protein, 8.2 Gm. per cent; plasma albumin, 4.35 Gm. per cent; plasma globulin, 3.85 Gm. per cent; nonprotein nitrogen, 20.6 mg. per cent; bleeding and clotting time, normal. X-ray of the arms, and legs revealed myositis ossificans progressiva.

Temperature continued between 100 and 101° F.; pulse rate between 80 and 100, with respirations around 24. At this time, a biopsy was done on the cystlike mass over the rib and the draining area on the left posterior thigh. Report was as follows: "There is obviously a change going on in the tissues which predisposed to the formation of calcium and to an attempt in this calcium formation to the formation of actual bone. Most of the reaction is calcific in character, and along with it, there is an increase of fibrous tissue. There is chronic inflammation as evidenced by the presence of mononuclear cells and lymphocytes along with giant cells. Much fat necrosis is present."

Fig. 3.—X-ray of extremity demonstrates placques of bone in soft tissue.

SUMMARY

In this report, we have given a review of the most important factors associated with myositis ossificans progressiva, and a presentation of another case. This case has followed the usual course, the malady beginning as an attack of acute rheumatism with progression and later a partial ankylosis of the neck, shoulders, and spine, and the formation of bony layers. This child is unusual in that he is one of the 25 per cent that presents no congenital anomalies. Current investigators state that the disease is most probably embryonic in origin. The nature of the dystrophy is still obscure, and the treatment is unsatisfactory.

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ERYTHROBLASTOSIS FETALIS

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ERYTHROBLASTOSIS fetalis is the broad clinical picture in which are included several clinical entities: (1) anemia of the newborn, (2) icterus gravis neonatorum, (3) hydrops fetalis.

The incidence of anemia of the newborn is difficult to ascertain. Mild cases may go unrecognized, or are considered as physiologic icterus, for mild jaundice often precedes anemia. The outstanding characteristic of congenital anemia is pallor of the skin and mucous membranes. Though this feature is apparent at birth it is generally obscured by jaundice. With recession of icterus, whiteness of the skin becomes pronounced. Pallor of the mucous membranes is noteworthy. The infants are listless, weak, and nurse poorly. Enlargement of the liver or spleen or both is noted, but generally to a lesser degree than observed in icterus gravis or hydrops. It was found in all our cases. There is no edema. Petechial hemorrhages of the skin are noted in the literature but were not present in our group. The diagnosis of anemia of the newborn is easily established by the clinical signs as noted herein and the characteristic blood picture. The prognosis is good, but the disease may run a prolonged course. Diamond, Blackfan, and Baty[1] indicate that the anemia may remain stationary or even become aggravated until the sixth week of life. At this time there is a return of a normal number of young erythrocytes. Finally, the hemoglobin and red cells increase to the normal though a four-month interval may be required for complete restoration.

Icterus gravis neonatorum designates that clinical form of erythroblastosis in which jaundice is the most prominent symptom. Edema is supposedly lacking, but in our series are included five infants presenting circumscribed swelling of the subcutaneous tissues.

The most prominent symptom of icterus gravis is jaundice which may be present at birth or be delayed for from twenty-four to forty-eight hours after delivery. A saffron yellow vernix caseosa arouses suspicion. In our series the infants were jaundiced at birth. The infants are generally listless, apathetic, and feed poorly. As the disease progresses, stupor and convulsions appear. In the terminal stages, vomiting, dyspnea, cyanosis, and frothing of blood-stained fluid are frequent manifestations. Cutaneous hemorrhage is not uncommon. Though jaundice may be intense, the mucous membranes are not uncommonly pallid. Enlargement of the liver and spleen affords palpation of these organs for varying distances below the costal margin.

Pregnancy associated with icterus gravis shows a greater incidence of toxemia. Hellman and Hertig[2] report two mild cases in nineteen mothers.

The diagnosis of icterus gravis is, therefore, easily made. Jaundice, an enlarged liver and spleen, and an increased number of nucleated red cells form a diagnostic triad. A golden yellow vernix if present at birth is indicative of the illness. Icterus gravis should be anticipated in a mother presenting a history of repeatedly stillborn infants without apparent cause or where a history of previous erythroblastosis is obtained.

Clinically, hydrops fetalis is the most severe form of erythroblastosis. A stillborn infant or death after feeble respiration is the rule. The longest life period recorded is six days. The infant presents a waxy skin with multiple zones of cutaneous hemorrhage. Edema is marked. Jaundice is occasionally noted. The face is enlarged and swollen, the neck short, and the abdomen markedly distended. The latter results from the presence of free fluid in the abdominal cavity and enlargement of the liver and spleen which are felt for varying distances below the costal arch.

The diagnosis of hydrops fetalis is easily established at birth by the clinical appearance of the infant and confirmed by study of smears made from cord blood. Even before delivery, an amber colored amniotic fluid directs suspicion. Intrauterine diagnosis can be made by x-rays as first shown by Hellman and Irving.[3] In the roentgenogram, the subcutaneous tissues are definitely thickened and show marked density. A corona surrounds the bones of the skull due to marked edema of the scalp.

These three conditions are related and differ only in the severity of the underlying pathologic findings. The mildest is the congenital anemia from which recoveries occur spontaneously, or better still, recover fully with transfusions. In icterus gravis the recovery is about 75 per cent, while in the severe form, hydrops fetalis, the infant with universal edema, the result is fatal.

A study of the literature gives us some very interesting clues as to the etiology of this condition.

Schwartz and Levine[4] studied the incidence of erythroblastosis in 2,000 deliveries and found that of 162 stillbirths or neonatal deaths, seven were definitely caused by erythroblastosis and six more probably resulted from this disease. They believed that the incidence will prove to be about 1 to 200 deliveries if estimated on the basis of Rh tests. Levine[5] had previously postulated that effects of isoimmunization by the Rh factor would be found to be more frequent, especially if serologic Rh tests were applied in cases of stillbirths and some cases of miscarriage.

Potter and associates[6] state that although about 12 per cent of all marriages will be between Rh-negative women and Rh-positive men, with a corresponding 12 per cent possible incidence of erythroblastosis, they have found erythroblastosis is only about 0.1 per cent of all pregnancies. Levine[5] also emphasized the discrepancy between the potential incidence (13 per cent of all matings, according to his figures) and the actual incidence, attributing this difference to the current tendency to small families, which reduces the chance of isoimmunization by successive pregnancies; and to the variations in the ability of Rh-negative women to produce immune anti-Rh agglutinins in response to the stimulus of Rh-positive cells.

Darrow,[7] in 1938, had suggested a hereditary transmission of the disease with transmission of a destructive influence from mother to fetus through the placenta. When, in 1939, Levine and Stetson[8] discovered an atypical agglutinin in the serum of a mother who had delivered a macerated fetus and later suffered severe transfusion reactions with supposedly compatible blood, and it was found that this factor agglutinated the blood of the majority of group O donors, the stage was set for the clarification of the erythroblastosis problem. The agglutinin was active at both 20° and 37° C., in contrast to the usual atypical agglutinins which are generally inactive at 37° C. Tests of the serum made a few months after delivery showed weaker agglutination reactions, and a year later all traces of the reaction had disappeared.

In January, 1940, Landsteiner and Wiener,[9] continuing their researches on rabbit immune sera produced with blood of Rhesus monkeys (which had previously been found able to react with human blood which contains the agglutinogen M) found that another individual property of human blood, which they designated Rh, could be detected with some of these sera. When anti-Rh sera become available, these were used by Levine in tests on the patient reported by himself and Stetson in 1939,[8] and proof was obtained that the factor involved was Rh and the maternal agglutinin was anti-Rh.

On the basis of Levine's work, it is now established that erythroblastosis is caused by isoimmunization of the mother by a dominant hereditary blood factor in the fetus, most often the Rh factor. In more than 90 per cent of the cases in which erythroblastosis develops, the mother's blood does not contain the factor Rh, while the blood of the father and fetus does contain the factor. Thus the mother is Rh negative and the father and fetus are Rh positive. "The two essential steps in the pathogenesis of erythroblastosis fetalis are (1) the response of the Rh negative mother to the foreign Rh positive fetal blood by production of anti-Rh agglutinins and (2) the continuous passage of maternal Rh agglutinins through the placenta to react with and hemolyze the susceptible fetal Rh positive blood." The foreign Rh-positive fetal blood cell—a formed element—enters the maternal circulation in sufficient quantity to stimulate the mother to produce anti-Rh agglutinins, but Levine[10] states that it now appears that only minute amounts of blood are required to give rise to this reaction, and that thus microscopic breaks in the fetal villi rather than gross lesions in the placenta may allow enough fetal blood to pass to get up the isoimmunization. In an experiment with the production of anti-M agglutinins in rabbits it was found that weak anti-M agglutinins could be produced by total volumes of 0.0014 and 0.0028 c.c. of blood, respectively. These small amounts, according to Hertig, whom Levine quotes, could pass through villi damaged by breaking off of fragments or terminal branches, though such a phenomenon has not actually been demonstrated.

"Once anti-Rh agglutinins have been produced they pass readily through the placental barrier to act on the susceptible Rh positive fetal blood. There is no difficulty in accepting this view since it is generally recognized that maternal antibodies are the source of the passive immunity normally observed during the neonatal period."[11]

The discrepancy between the relatively large number of marriages of Rh-positive men to Rh-negative women, estimated at about 13 per cent of all marriages, and the low incidence of erythroblastosis, namely about 0.1 to 0.2 per cent of births, demands some explanation. Apparently the presence of the factor in the husband and its absence in the wife are not always sufficient to cause the disease in the child. Several explanatory considerations have been discussed:[6] (1) Variations in the permeability of the placenta may hinder or facilitate the passage of the Rh-positive factor from the fetus to the mother and of specific anti-bodies from the mother to the fetus. (2) More than one pregnancy may be required to induce an adequate degree of immunization of the mother, just as several series of immunizing injections may be necessary to build up immunity in animals. The rarity of erythroblastosis in the first-born points in that direction. The modern tendency to restrict the number of children may thus be one of the reasons for the disproportionately low incidence of erythroblastosis. (3) Recent reports indicate that the disease may occur in mild form and that some cases may escape recognition. (4) Men who have inherited the

Rh factor from one parent only, that is, heterozygous fathers, do not transmit the Rh factor to all children, and the children who do not inherit the factor escape erythroblastosis. This possibility is illustrated by the recent report of erythroblastosis in the Rh positive twin, and the other twin, Rh negative, remaining unaffected.[9]

To these attempts at explaining the apparent relative rarity of erythroblastosis, Race and Taylor[13] bring forward one more. They claim that the majority of fathers of erythroblastotic infants are homozygous, that is, inherit the Rh factor from both parents, which would reduce considerably the possible incidence of the disease, since only about 43 per cent of all Rh-positive persons are homozygous. The calculated frequency of marriages of homozygous Rh-positive men with Rh-negative women is about 5.69 per cent, as compared with about 13 per cent if all Rh-positive men were included. In the serum of an Rh-positive mother of an erythroblastotic infant Race and Taylor found an agglutinin for blood corpuscles of Rh-negative persons and of heterozygous Rh-positive persons. They assume that this agglutinin reacts with the recessive hereditary factor (gene rh). The serum in question did not react with 20 per cent of blood samples. Now, an Rh-negative woman married to a homozygous Rh-positive man whose red cells are not clumped by such serum is less likely to give birth to a second or later child without erythroblastosis than if she is married to a heterozygous Rh-positive man.

Levine[14] states that isoimmunization may occur even in the absence of demonstrable antibodies. It may be assumed that antibody production has occurred, but since the antibodies are fixed to the cells of the reticuloendothelial system they are not released into the circulation.

Theoretically it would seem that isoimmunization could occur in an Rh-negative child of an Rh-negative father and Rh-positive (heterozygous) mother, but it is assumed that this does not occur, because as is well known, infants produce antibodies very poorly.

In the 10 per cent of cases in which erythroblastosis cannot be attributed to isoimmunization by one of the Rh factor variants, and in which the mother's blood is Rh-positive, Levine and Polayes believe that the isoimmunization is reduced by other factors of human blood such as A, B, and "Hr"; "anti-Hr," is Levine's designation for an atypical agglutinin, seemingly related to the Rh factor, found in an Rh-positive mother who had borne an erythroblastotic infant.

In clinical medicine the Rh types serve to explain a certain number of the hitherto puzzling instances of hemolytic transfusion reactions in Rh-positive patients and the occurrence of erythroblastosis fetalis in certain Rh-positive infants with Rh-positive mothers.[15] In the cases in which isoimmunization has occurred between different Rh blood types, the use of Rh-negative blood is indicated for the same reason that group O blood can be used for individuals of groups A, B and AB in ordinary blood transfusions.

Illustrative of the typical cases found in erythroblastosis are as follows:

CASE 1.—Mother (B), service case delivered at Brooklyn Womens Hospital; aged 26 years, para iii; low-forceps delivery, full term.

Infant (B), male, born Jan. 7, 1944, birth weight 6 pounds, 2 ounces, one day old, born in a pool of amniotic fluid. Jaundice appeared on second day. Blood smear showed nucleated cells, 218 to 100 white blood cells. Spleen nonpalpable, liver not unusually enlarged for infant. The red blood cell count was 1,500,000. Hemoglobin was 102 per cent.

The mother was Rh negative. The infant was Rh positive. The father was Rh positive. After three transfusions of 75 c.c. Rh-negative matched blood, the infant made an uneventful recovery. On discharge the red blood cell count was 3,450,000. Hemoglobin was 76 per cent.

CASE 2.—Mother (G), service case delivered at Beth-El Hospital, aged 38 years, para v, gravida vi, stillbirths 1, spontaneous delivery.

Infant (G), female, born Oct. 27, 1943, birth weight 7 pounds, 11 ounces.

Oct. 27, 1943. The baby was admitted to the nursery, markedly jaundiced and showed some cyanosis around the lips. Within two hours after admission a blood smear showed 300 nucleated cells to 100 white cells. Transfusion was ordered and given within two hours of admission, 60 c.c. of Rh-negative matched blood transfused into a scalp vein. Prothrombin time was 72 seconds Quick method, normal 12 seconds.

Oct. 28, 1943. Cyanosis and air hunger still present. Marked icterus to the skin and sclera. Prothrombin time was 120 seconds quick method, normal 13 seconds. Liver and spleen moderately enlarged. Two days later a complete blood count and smear were taken and showed as follows: 15.4 Gm.= 100 per cent hemoglobin, red blood cells, 2,500,000; white blood cells 54,000, 150 nucleated red blood cells.

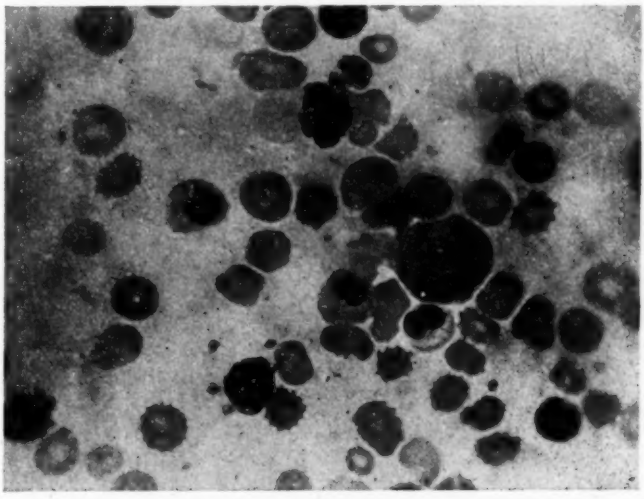

Fig. 1.—One normoblast in the stage of mytosis. Few megaloblasts and a few normoblasts. Two myeloblasts. (Myeloid series always appears in cases of erythroblastosis.)
Background: Hemoglobin and red blood cells were very low; therefore, there is macrocytosis of the red cells. Some poikilocytosis, anisocytosis, and hypochromia of red blood cells.

Oct. 29, 1943. Child was given another transfusion of 60 c.c. Rh-negative blood.

Oct. 30, 1943. A third transfusion of 65 c.c. citrated Rh-negative blood again given into a scalp vein. Prothrombin time 54 seconds Quick method, normal 12 seconds. Four days after delivery a complete blood count showed: 10.5 Gm. = 68 per cent hemoglobin; red blood cells, 3,500,000, 8 nucleated; and white blood cells, 9,000.

There was a marked improvement noted in the child's general condition. Icterus was clearing. Because the hemoglobin was below 75 per cent the infant was given another transfusion of 60 c.c. Rh-negative blood into a scalp vein. Prothrombin time dropped to 29 seconds Quick method, normal 12 seconds.

Nov. 3, 1943. Prothrombin time 19 seconds Quick method, normal 13 seconds. The infant by now was taking her feedings well. Skin was clear. Aqueous solution Aquanone Vitamin K (Bischoff) 1,000 units per cubic centimeter (ampule form) one-half cubic centimeter injected into each arm was given twice daily during her stay in the hospital because of the prolonged prothrombin time.[13]

Nov. 4, 1943. Report from the laboratory revealed that the blood of the baby was Rh positive; father, Rh positive; mother, Rh negative.

Nov. 8, 1943. On discharge the baby's weight was 8 pounds, 13 ounces. Skin was clear, no icterus. Final blood count was as follows: 12 Gm. = 78 per cent hemoglobin; red blood cells, 3,580,000, 2 nucleated; and white blood cells, 10,500. The infant was discharged to home surroundings and from recent report is doing well.

Contrast these two cases with the following in which we encountered difficulties due to transfusion reactions.

CASE 3.—Mother (L), delivered by Dr. Bloom at the Beth-El Hospital, aged 33 years, para ii, midforceps delivery, full term, apparently normal infant.

Infant (L), male, born May 2, 1944, birth weight 9 pounds, 5 ounces; height, 23 inches.

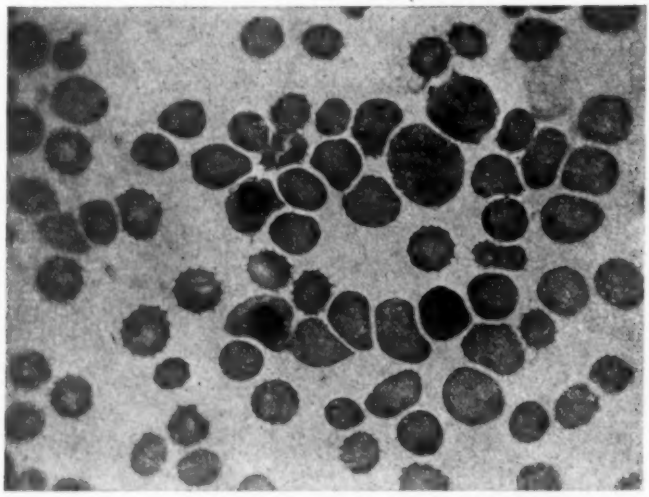

Fig. 2.—Few normoblasts; two myeloblasts.
Background: Hemoglobin and red blood cells were very low; therefore, there is macrocytosis of the red cells. Some poikilocytosis, anisocytosis and hypochromia of red blood cells.

May 3, 1944. Within twenty-four hours the infant developed jaundice with difficult respiration of a crowing nature. Physical examination was essentially negative except for a palpable liver and spleen. Rh factors determined on father, mother, and infant revealed that the father was Rh positive, the mother was Rh negative, and the infant was Rh positive. Blood examination of the infant was: hemoglobin 7.0 Gm. or 45 per cent; red blood cells, 2,250,000.

A blood transfusion to the infant of 90 c.c. compatible citrated Rh-negative blood was given by the gravity method into a scalp vein with no immediate reaction. Child was given continuous carbogen.

May 4, 1944. Infant became cyanotic and Coramine M III was given. Infant appeared better. The temperature all this time was normal. Complete blood count was as follows: hemoglobin, 9.6 Gm., or 62 per cent; red blood cells, 3,250,000; white blood cells, 9,000; differential was normal; platelets, 290,000; nucleated red cells, 10.

May 5, 1944. Infant was given 90 c.c. compatible citrated Rh-negative blood transfused into a scalp vein. There was no immediate reaction, but a reaction was noted in one and one-half to three hours by temperature elevation to 102° F. The following day the temperature fluctuated between 100 and 102° F., returning to normal at 8 P.M.

May 7, 1944. Temperature was normal. Child's jaundice increased. The respiration was still rapid and labored.

May 8, 1944. Slight improvement noted. Complete blood count was taken. Hemoglobin, 8.5 Gm., or 55 per cent; red blood cells, 2,750,000; white blood cells, 14,000; differential, increase in leucocytes to 36 per cent; monocytes to 5 per cent; platelets, 290,000.

May 9, 1944. Infant was given 100 c.c. compatible Rh-negative blood transfused into a scalp vein. There was no immediate reaction. Within five to eight hours the temperature fluctuated between 100.8 and 101.4° F. The temperature remained elevated all that day reaching a maximum of 104.6° F.

May 10, 1944. Blood count revealed: hemoglobin, 8.5 Gm., or 55 per cent; red blood cells, 3,050,000; white blood cells, 20,000; differential, increase in neutrophilic toxic granules; platelets, 300,000; nucleated red cells, 2.

May 11, 1944. Infant was transferred from the nursery to the Children's Pavilion. Physical examination revealed edema of the scrotum, feet, and thighs. The infant was still jaundiced and there was a slight tenseness of the fontanels. Medication: 2 grains sulfadiazine, 5 grains sodium bicarbonate every four hours.

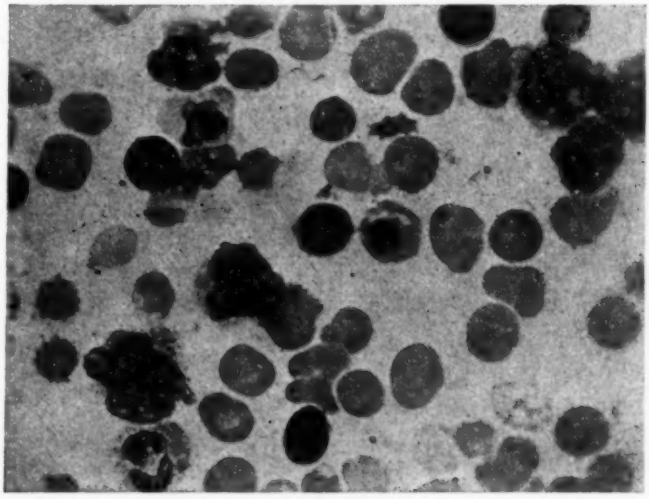

Fig. 3.—Metamyelocytes and one nucleated red cell.
Background: Hemoglobin and red blood cells were low; therefore, there is macrocytosis of the red cells. Some poikilocytosis, anisocytosis, and hypochromia of red blood cells.

May 12, 1944. Edema progressed and also swelling of the lips and eyelids. Some extravasation of blood about the eyelids. Tenseness of the fontanels remained the same.

May 13, 1944. Complete blood count revealed the following: hemoglobin, 7.5 Gm., or 48 per cent; red blood cells, 2,250,000; white blood cells, 50,000; differential, increase in neutrophilic toxic granules, shift to left of white blood cells; platelets, 290,000; nucleated red cells, 3. Infant was given 100 c.c. Rh-negative blood, type O, with low titer of B.

May 15, 1944. Edema decreased but infant's condition was still grave.

Two days later recurring edema of the lips, thighs, scrotum, and back became evident. There was slight improvement in the color of the skin. Hemoglobin, 9.5 Gm. or 62 per cent; red blood cells, 3,050,000.

May 18, 1944. Ninety cubic centimeters plasma strained from compatible Rh-negative blood were given. The infant stopped breathing at completion of the transfusion, but after artificial respiration and stimulation with adrenalin the infant seemed to improve but soon thereafter took another turn for the worse. The infant expired twenty-four hours later, seventeen days after birth.

Despite the transfusions the condition of the infant became progressively worse. There is little doubt that transfusion reactions and factors other than Rh prevented this infant from making a recovery. An autopsy was performed.

Autopsy Report.—Baby L, nine hours post mortem.

Body is that of a well developed and nourished white male infant 53 cm. and weighing 4,340 Gm. Body is diffusely icteric.

Chest: The right pleural cavity contains about 10 c.c. of thick greyish yellow odorless pus loculated between the upper and lower lobes in the midposterior surface and extending into the lower lobes as an abscess covered by a greyish pyogenic membrane, the abscess approximately 3 cm. in diameter. About 50 c.c. of thinner but otherwise similar pus is free in the pleural cavity and the visceral and parietal pleura of all the right lobes, but particularly the lower lobe is covered with a greyish fibrino purulent exudate, the pleurae loosely adherent. On section all the lobes contain numerous small firm airless greyish areas; these are confluent in the lower lobe to attain a size of approximately 2 cm. in which instance the central portions are softened and semifluid; no relation to the bronchus is apparent. In the left lung chiefly in the lower lobe are occasionally scattered similar airless pneumonic areas; the pleura is not involved. The tracheal bronchial tree, except for marked congestion and icterus of the mucosa, is grossly unaltered. The right lung weighs 75 grams; the left, which is generally well aerated, 36 grams. The heart weighs 35 grams; the pericardium is moderately icteric and contains a small recent ecchymosis. The myocardium is pale and somewhat flabby, the endocardium similarly contains a few small recent ecchymosis. The valves and the aorta and branches are grossly unaltered. The foramen ovale is widely present.

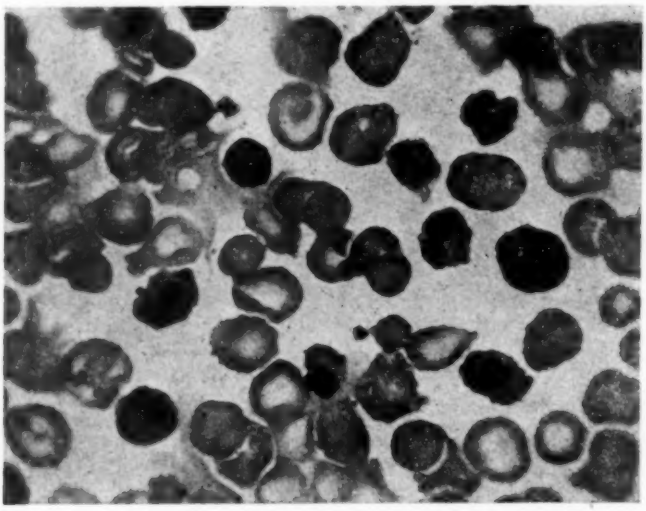

Fig. 4.—Typical picture of erythroblastosis. Megaloblasts, some in the stage of mytosis. Some of the myeloid series, some normoblasts.

Background: Hemoglobin and red blood cells were low; therefore, there is macrocytosis of the red cells. Some poikilocytosis, anisocytosis, and hypochromia of red blood cells.

Abdomen: About 100 c.c. of slightly icteric tinged fluid is freely present in the peritoneal cavity. Liver weighs 285 grams, surface is smooth and glistening and on section lobular architecture is poorly defined but regular where seen in the congested icteric cut surface.

Gall Bladder: The gall bladder is thin walled, distended with about 2 c.c. of viscid bile, but is otherwise grossly unaltered and the bile ducts are patent and grossly unaltered. Pancreas weighs 7 grams, is firm and well lobulated throughout. Spleen weighs 52 grams, capsule is smooth and tense and on section cut surface is rubbery, deep mahogany in color with follicles and trabeculi not visible.

Kidneys: The kidneys are represented by a horse-shoe kidney, the fusion at the lower pole, the ureters crossing anteriorly. The right kidney has two distinct ureters which fuse just below the right border of the fused kidneys but which have separated not connected the renal pelves. On section the kidneys show pronounced fetal lobulation and marked icterus but otherwise unaltered, and the ureters, except as noted, are grossly unaltered as is the bladder save for moderate numbers of small ecchymosis into the bladder mucosa. The right adrenal weighs 2 grams; the left, 5 grams; neither is grossly altered. Gastrointestinal tract shows no gross anatomic changes.

TREATMENT

The following procedures are recommended:

1. Blood specimens for determination of Rh factors taken from the mother at the same time as blood for Wassermann, usually in the second or third month of pregnancy.

2. Blood smears for erythroblastosis from the infant at the time of delivery.

In cases of hemolytic anemia in which transfusions with Rh-negative blood was successful after several unfortunate experiences with Rh-positive blood, Poncher and associates[17] suggest that in all cases of hemolytic anemia, in which repeated transfusions are necessary with consequent greater opportunity for isoimmunization of Rh-negative patients, more sensitive cross-matching procedures than usual should be employed, for determination of the Rh type of the patient. (However, agglutination is not always demonstrable by cross-matching, as shown by Levine.[14]) Dameshek and Levine[15] also reported violent transfusion reactions in an Rh-negative patient with acquired hemolytic anemia and caution that the first few transfusions should not be given because of the danger of isoimmunization.

At about the same time, Diamond[19] suggested that "patients who are likely to have repeated transfusions should be typed for Rh factor, to avoid immunizing Rh negative persons by the use of Rh positive blood. This is especially important in women of childbearing age, to avoid the possibility of harming an Rh positive fetus at a later pregnancy." Diamond also re-emphasized the danger of using the husband as a donor for transfusions in mothers of erythroblastotic infants, and urged the building up of lists of Rh-negative donors, and the establishment of laboratories for carrying out typings for the Rh factor in order to obtain these donors and to determine the need for Rh-negative blood in a given case.

Wiener and Wexler[20] caution that in hemolytic anemia of the newborn transfusions of blood from the mothers are contraindicated because of the additional antibodies which would be introduced; that the father's Rh-positive blood (or that of any other Rh-positive donor) should not be used because the tissues of the infant contain enough stored antibodies to destroy any additional Rh-positive blood; and that the infant should not nurse, since antibodies may be transmitted through the colostrum and milk. They give 10 c.c. of blood per body weight (usually about 75 c.c.) from group O Rh-negative donors; this is repeated on the next day and these two transfusions usually suffice, since even if all of the infant's own blood cells are later hemolyzed, the donor's blood remaining contains enough erythrocytes to give the infant a hemoglobin of about 60 per cent, which will tide him over the period during which the Rh antibodies are being eliminated from the body. During this time, blood grouping tests will show the donor's type, and few or none of the infant's own cells. Later, the donor's cells are replaced and the infant's type again becomes apparent.

In a discussion of this paper Dr. Jacob Halperin brought out the following significant facts:

Dr. Jacob Halperin reviewed 3,885 cases that were delivered at the Beth-El Hospital, for a period of eighteen months. In this group there were ninety-four stillbirths, and of the unexplained deaths (stillbirths), there were forty-six males and twenty-seven females. Forty of the newborn infants developed erythroblastosis or anemia, or jaundice; and of these, twenty-six were males and

fourteen were females. Eleven of the erythroblastotic babies died; of these, ten were males and only one was a female. In one that did not come to autopsy the sex could not be determined. The mothers of the above dead babies were all Rh-negative, except in one instance where the mother was positive. Routine determination of the Rh factors in all obstetric cases were: In the first 500 determinations they found sixty-six Rh-negative women, an incidence of 13.2 per cent. According to his statistics, they found that *males* are more prone to develop erythroblastosis in the *ratio of 3.1;* and of the *fatal cases 5.1.*

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AVOIDING BEHAVIOR PROBLEMS

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INTRODUCTION

SERIOUS behavior problems seldom arise abruptly in later childhood. The maladjustment in the child and the tension between him and his parents have usually accumulated step by step as the child passed through successive stages in his development. In tracing the origins of emotional disturbances, one encounters again and again stories of friction developing in infancy and early childhood around certain typical everyday situations. The commonest are: feeding, weaning, thumb-sucking, toilet training, anxieties incidental to development, sibling jealousy. It is helpful for physicians to know ahead of time where and when these difficulties are likely to arise and to give routine advice calculated to avoid or minimize them.

EARLY FEEDING PROBLEMS

Feeding problems seem to be the commonest behavior disturbances among American children. They not only cause much unnecessary malnutrition but also create tensions in mother and child which often predispose to other emotional disturbances outside the field of feeding. A majority of these problems begin during the first two years in the child's life. This is the age in which to expend the greatest prophylactic effort. It is during this period that the infant most regularly and frequently comes under the care of the doctor and nurse.

An early occasion for a feeding problem arises if the mother takes home her new baby along with a formula which is a little too large. When the baby, blissfully satisfied, falls asleep, the mother, instead of being pleased, holds the bottle up in alarm to see how much is left. She attempts to awaken him again by snapping the soles of his feet. When he opens his mouth to squawk she reinserts the nipple. If he tries to go to sleep again she stirs the nipple vigorously in his mouth.

Probably the reason that more problems do not develop in this newborn period is that the baby's appetite is increasing so fast that he catches up to the formula in a few days, usually before his mother has taken away his appetite completely. Occasionally, however, a feeding problem becomes well established at this early stage, more often in the case of the premature baby, because of the inverse ratio between the baby's size and the mother's anxiety. If a child has been systematically robbed of his desire for food from the very outset, the mother may be quite truthful when she reports that the child, now 5 years of age, has never shown any appetite.

Prevention is always easier than cure. The mother in the hospital is in a state of relative relaxation and calm compared to the tenseness which is so

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This article is based on material presented in in-service training courses for physicians and public health nurses, instituted by the Bureau of Child Hygiene of the Department of Health of New York City. The material has been kept in a semiconversational tone in which talks of this kind have been given during the past four years and the language may therefore from time to time seem somewhat arbitrary. It is the spirit of the presentations that is important and it should be realized that there was free discussion of most of the points that are presented. The topics discussed are those which experience shows are of chief concern to the 100,000 mothers who attend the well-child conferences each year.

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apt to envelop her when she takes her first baby home. This is the time to implant wholesome ideas about the naturalness of feeding and about the baby's capacity to know his caloric needs. The physician can refer casually to the formula as a rough approximation of what will satisfy the baby's hunger. Specifically he must explain that the baby will be a better judge than parent or scientist of the quantity he wants at each feeding, that the parent should not try, after the baby is no longer eager, to get in one more drop.

While he is suggesting a casual attitude toward bottle feeding he might well discuss also the philosophy of the feeding schedule. Infant feeding during the last forty years has been dominated by the idea of extreme regularity. This was a natural development in a phase devoted to bringing scientific order out of the ignorance and confusion of the past. But gradually an awareness has arisen that the swing to regularity has gone too far, that the insistence on rigid routine ignored the variations in functional capacity of individual babies and created, at least temporarily, frustration in those who had difficulty conforming to the schedule. Long-lasting has been the harmful effect on countless mothers who have been encouraged to become tense, authoritative, and intolerant in their attitudes toward their children.

The pendulum has begun to swing in the opposite direction. Various physicians, parents, and psychologists in rebellion against arbitrariness are experimenting with the so-called "self-demand schedule" according to which the infant is fed whenever he appears hungry. The clock is determinedly ignored.

Only time will show how far the pendulum will swing and how acceptable the method will prove to be. At the present time, the implication of anarchy in the method disturbs many who forget that until the twentieth century the young of the entire human race, in common with the rest of the animal kingdom, always determined their own feeding time without disastrous results.

As a matter of fact, observations of infants fed at their own demands indicate that most babies put themselves on a "regular" schedule very shortly. The baby may take a five-hour interval at one time of the day and a three-hour one at another time, but the pattern tends to repeat itself day after day, and the baby is on a regular schedule which is not predetermined by the physician and mother.

But even if we eventually go back to feeding at the infant's demand, it should be recognized that there will be a transition period, and that at least part of this generation of mothers imbued from their own infancy with the moral obligation of regularity cannot suddenly be cast adrift with the advice to feed the baby when he is hungry, without feeling insecure. There are other busy mothers for whom regularity has great practical value. It seems possible to retreat from the rigidity of the recent past, to allow for individual variations in both babies and parents, and still give the mother a framework of schedule within which to work. The mother might be told the following before she assumes the care of her infant:

"The feeding schedule is primarily for your convenience and to guard against excessive overfeeding. It is not a moral law. One baby adjusts to the four-hour interval from the start, another takes weeks to become regulated. You can wake the baby if he is asleep when feeding time comes. This seldom arouses balkiness because young infants, waked after four hours, will always show hunger within a few minutes. But if he wakes half an hour early or an hour early on occasion, and seems really hungry, do not be afraid to feed him then. He may compensate by a longer sleep the next time so that you can get

back on schedule. Even if the schedule is accelerated all day, he will make up the time during the night. If he regularly is hungry in about three hours, he is a baby who temporarily needs a three-hour schedule. If he wakes at 2 A.M. or thereabouts, feed him. This does not establish a habit. All babies will give up the 2 A.M. feeding as soon as they are getting enough calories at the other meals to allow them to sleep through the night. Some babies can do this at the age of one week, others not until they are a month old." Such middle-of-the-road advice not only gives the mother who wants definiteness a tangible pattern to aim at, but also makes allowances for the baby's need. The mother who prefers to let the baby dictate can construe this system very liberally.

In attempting to remove some of the unwholesome apprehensiveness with which the new mother is apt to face the whole matter of the formula and the schedule, it is helpful to ask her to imagine how baby feeding proceeds in a primitive society without pediatricians or cows. The baby sleeps until he is hungry. He wakes and cries. The cry does not just give vent to the baby's feelings but also arouses a sense of urgency in the mother. In putting him to the breast she relaxes the tension in the baby and in herself. The baby nurses until he is satisfied and that satisfies the mother too. She does not worry about how much he has taken or about how much he has left. If a mother can visualize this picture at all, it will help her to understand that a civilized baby might also be trusted to take only as much as he wants at each feeding, to understand that minor irregularities in schedule do not violate the laws of nature or create spoiled personalities.

A more common time for the beginning of a feeding problem is when solid foods are first introduced. Most babies are at best doubtful about the first few mouthfuls. They wrinkle their brows, screw up their faces, and clack their tongues against the roofs of their mouths with at least a shade of disgust. The food is oozed out onto the chin. This bewilderment is understandable. The taste is strange, the consistency is strange, and the spoon is strange.

After two or three days the majority of babies seem to decide about cereal, which is the traditional first food, "It's strange but it's calories so I will take it." Within a week or two they are enthusiastic. But there are other babies who, on the second day, dislike the cereal more than on the first day, and on the third more than the second. If the mother persists in her efforts to force the substance in, the baby's obstinacy increases apace. When such a struggle has lasted for ten days the mother may call the physician with considerable alarm to say, "Doctor! Not only has the baby refused to take his cereal but this morning he refused his bottle too!" This example of how resistance once thoroughly aroused will spread to other areas, throws light not only on the development of feeding problems, but also on other behavior problems as well.

To prevent this battle over the first solid food the mother can be advised at the time the solid food is prescribed, "Take it easy. It will require several days, perhaps several weeks, for the baby to get familiar with and enthusiastic about this new food. There's no hurry. The only important thing is to ensure that he will eventually like it. A mere taste a day is plenty until he becomes eager."

Cereal so often causes rebellion that I have in recent years routinely suggested a fruit like applesauce or mashed banana as the first solid food. Fruit is nearly sure-fire. The baby may be puzzled for a day or two, but then almost invariably becomes enthusiastic. After a couple of weeks when he has become thoroughly prejudiced in favor of the idea of solid food, cereal can be added

too. He is now in a mood to take cereal or anything else equally unpalatable. Whereas if he has started with cereal and has fought it for two weeks, he will in turn fight fruit or any other delicacy on principle.

The time when feeding problems most commonly begin is around the age of one year. The 6- or 9-month-old baby is usually so hungry at mealtime that he opens his mouth and leans forward for whatever his mother puts on the spoon. Many 12- or 15-month-old children lose this avidity, at least in spells. They have time to ask themselves, "What appeals to me today?" Another factor is the growing egotism and negativism which are normal and desirable developments at this age. The less ravenous appetite and the increasing arbitrariness in expressing choices bring to the surface the normal and sometimes surprising variations in appetite, which Davis[1] observed in her experiments on self-selection of diet by children.

The conscientious, well-instructed mother cannot "take it." She knows something about what a well-balanced meal consists of and she has been led to believe that it is her duty to get it ingested. She complains bitterly and incredulously to the doctor, "Last week he loved his spinach best of all, but today he wouldn't even touch it." The foods most commonly refused or taken in reduced quantities are vegetables, cereals and milk. These three have always seemed to the mother the very foundation of health and growth. She dare not let them be slighted. She urges or forces. The baby's obstinacy increases. It is already too late to ease the situation completely at the next routine medical visit. Mother and baby both have their backs up. Each has become disillusioned about the other. All this is hard to undo.

The mother should be warned *before* the change occurs. In fact, it is wise to repeat the caution each time the baby is seen between 9 and 15 months. You say, "Don't be surprised if the baby's appetite falls off and he becomes more choosy. This is normal, otherwise he would become an obese monstrosity. He may turn against half his vegetables. Do not worry. Serve him the others. He may reject all his vegetables for days or even weeks. If this happens I wouldn't even serve them for two weeks. It will infuriate you to buy, prepare, and serve them only to have this whipper-snapper turn up his nose; and it will tempt you to try to force them. While he is off vegetables, serve him fruit twice a day. His fruit and his cod-liver oil will make up for the vegetables. He may temporarily cut down his milk intake to a pint a day or even less. A pint is enough anyway. If he goes below for any length of time you can serve it in milk puddings, milk-made cereal and cheese. His milk intake will probably go up again sooner or later if you don't turn it into an objectionable food by urging it. Instead of cooked cereal you can offer dry cereal, bread, potato, macaroni, tapioca, rice. Even if he wants none of these starches for considerable periods he will not suffer. If you will let your baby go on thinking of food as something always to be enjoyed, his nutrition will take care of itself, even though his appetite varies considerably in amount and in kind. But if during this period when he becomes more choosy you urge and force and make him feel that half the foods are his enemies, there's a good chance that you will make him thin and 'cantankerous.'"

There is one other occasion when feeding problems commonly begin and that is after an illness. A few days of a febrile disease may take all the color out of a baby's cheeks and a lot of the fat off his ribs. To the mother who has set great store by his plumpness and color this is deeply distressing. One day the fever is gone and the doctor says, "Now you can give him some cereal." The

mother is overjoyed. She brings in the cereal, all eagerness, but the baby gives it a fishy eye and turns away. His gastrointestinal tract tells him it is not ready for cereal yet. His mother thinks either that he has forgotten how or is too weak to eat and that she must get him started. Forcing food in the face of the anorexia of illness creates a disgust reaction even more quickly, more intensively, and more permanently than forcing during health. Again prophylaxis is better than belated efforts at cure. At the end of each of the child's first illnesses the physician would do well to remind the mother that it often takes several days for the appetite to recover, but that when it does return it will not only be intense enough to ensure the child's former rate of growth, but also it will probably be abnormally great to ensure the recovery of the weight lost.

WEANING CONFLICTS AND THUMB-SUCKING

A story of a stormy battle over weaning will often be found in the past history of children with severe behavior disturbances, suggesting that the kind of resentment created by this particular struggle may be unusually long-lasting and bitter. Certainly the pediatrician is familiar with the common complaint that a feeding problem centering around milk started abruptly at the time of an attempted weaning to the cup.

How should weaning be managed and at what age? Experience suggests that there is no simple or single answer. Babies are born with a strong instinct to suck quite apart from the instinct of hunger. In some babies this desire to suck appears to weaken and disappear in the last half of the first year. Others seem unwilling to begin to give up sucking until the first half of the second year. The baby will show in various ways how ready he is for weaning from breast or bottle, and it seems fair that his readiness should be the main guide of parent and physician. If one questions mothers of 8- or 9-month-old infants about their attitudes toward the bottle, toward the cup, and toward thumb-sucking, the answers fall between two extremes. Of one baby the mother will say, "He seems to be bored with the bottle. Half the time he only chews on it or plays with the nipple. When I offer him milk from a cup he takes it enthusiastically. He isn't doing any thumb-sucking." At the other extreme is the baby whose mother says, "Oh, Doctor! How he loves his bottle. All the time he is eating his food, he is watching the bottle out of the corner of his eye and when it's time for the bottle, he's all eagerness. He clutches and fondles it while he's drinking and always finishes it to the last drop. He's very suspicious of milk in the cup and will take only a sip at most. It's not that he doesn't know how, because he takes his orange juice well from the cup. He is doing a lot of thumb-sucking." Many babies of course fall between these two extremes, and the thumb-sucking is not necessarily so highly correlated with the other signs of sucking need.

For the sake of the discussion let us consider the two clear-cut types. The baby who at 8 or 9 months is getting bored with breast or bottle and is taking milk eagerly from the cup seems ready for weaning and it would seem entirely proper to tell his mother, "Gradually over a period of weeks, put more and more of his milk in the cup at each meal until the bottle is done with." Another gradual method is to substitute the cup for the bottle first at breakfast, then at lunch, then at supper, allowing a couple of weeks between each change. If during the process the baby shows reluctance to go further, the mother should follow his cue. There is often a temporary increase in the desire to suckle during illness, during the miserable stage of teething, or during any episode which upsets his spirits.

If the baby at 9 months still loves his bottle dearly and is suspicious of milk from the cup, present-day teaching emphatically advises against attempting to force the issue. Experience with forced weaning shows that many babies will react violently with an absolute and often long-lasting refusal to tolerate the cup. An occasional baby will go on a complete hunger strike for several days and another may become generally resentful and hostile. It is true that many babies who have been deprived of a bottle against their wishes, will, after holding out for two or three days, apparently decide to let bygones be bygones. But one cannot tell ahead of time which will give in and which will remain adamant. From the sharp distinction that many a baby makes between orange juice and milk from the cup, it is clear that he is not primarily suspicious of the cup itself. He apparently feels deeply that milk from bottle or breast has been and still is his chief emotional gratification and perceives that milk-in-cup is a threat to its continuance.

It will help to prepare the infant for eventual weaning to offer him a sip of milk a day from the cup beginning at 5 months. At that age he will try almost anything. At 10 months he has become wise enough and opinionated enough so that he is apt to object to anything newfangled on principle. Unfortunately, however, the babies who seem destined to be long sucklers may take the sip a day for several months and then turn sharply and indignantly against the cup at about the age of 10 months.

If a baby falls into the group of those who are still devoted to the bottle and suspicious of the cup at 9 or 10 months, the chances are good that he will stay of the same opinion until he is at least 14 or 15 months. Then he will relent gradually. But even when initial progress is good he is apt to want the supper bottle for several months more. It is important that during this age of suspicion of the cup, between, say 10 and 15 months, that the mother refrain from urging the cup or withholding the bottle, since this seems to increase his dependence on the bottle and postpone his readiness for weaning.

Thumb-sucking is obviously related to the sucking instinct and the problem of weaning. Until recent years it was universally considered just a bad habit which ought to be broken quickly before it became ingrained. Levy[2] collected evidence that the baby sucks his thumb because he has not gotten enough satisfaction from the breast or bottle, that babies whose bottles took a long time to empty were less apt to thumb-suck than those who drank their bottles quickly through large nipple holes, and that babies who had few nursings in the twenty-four hours were more apt to thumb-suck than those who had frequent nursings. He showed that puppies, deprived of the chance to suckle through being fed by a medicine dropper, sucked vigorously on various parts of their own and each others' bodies. I have repeatedly seen thumb-sucking begin at the period when an infant was able to reduce his bottle time from twenty to ten minutes because of his growing strength and the aging of the nipple, or when he was suddenly weaned to the cup at an early age. I have the impression that there are two other etiological factors. First, there seem to be wide constitutional differences in the amount of sucking craving in different babies. Second, the important time to insure complete sucking satisfaction is in the first three or four months of life. Many babies are unable to get their thumbs into their mouths except by accident before the age of 3 months and therefore can give their mothers only vague signs of their unsatisfied craving at the period when correction is most vital. Incidentally thumb-sucking that occurs only just before feedings seems to be merely an expression of hunger.

If thumb-sucking in early infancy is primarily the result of a deficit in sucking satisfaction at breast or bottle, the prophylaxis and treatment should consist in providing longer and more frequent opportunities to nurse. For the breast-fed baby this means allowing him to nurse as long as he feels the urge rather than stopping at any arbitrary number of minutes. Sometimes a baby taking both breasts at each feeding and being removed after ten minutes on the first, stops spontaneously after five minutes on the second because he is too full (with the initial copious flow), even though he has not had his quota of sucking. In a few cases this can be solved by prolonged nursing at only one breast. But if the milk is insufficient at least the baby can be allowed to nurse much longer on the first breast before being shifted to the second.

Just as soon as the bottle-fed baby begins to suck his thumb, or, more important, shows signs of *trying* to, one should inquire whether he has recently been able to drain the bottle in a shorter time and suggest a new set of nipples with smaller openings.

Occasionally one can suggest more frequent feedings in the young infant if he is willing to take them and his mother to give them. Few mothers, however, take kindly to the idea of reverting to a three-hour schedule unless they are excessively alarmed by thumb-sucking. It is sensible though, when the baby is beginning to thumb-suck, to advise against omitting the 10 P.M. and the 6 A.M. feedings for a while longer, even though the baby seems ready for the change in other respects.

If the feedings are lengthened or made more frequent and the thumb-sucking still persists, the hypothesis that the baby is trying to make up insufficient nursing time will dictate emphatically that no effort should be made to interfere with the thumb-sucking. The aim, of course, should be to give the baby every opportunity to suck by any means that he can use.

By the time a baby is a year old thumb-sucking appears to be no longer primarily a need to satisfy the sucking instinct but has become a comforter. He no longer sucks it a certain number of minutes every day but only on special occasions: when he is going to sleep, when he is fatigued, when he is frustrated, when he is bored. There is no longer any point in trying to increase his nursing time. The constructive thing with the 1-, 2-, or 3-year-old child is to survey his daily life to see whether he has enough playthings, play space, and playmates to make life absorbing. Is he being treated at home in such a way that he feels secure and happy? Whether or not constructive changes can be made in his daily routine and handling, it seems wise to advise the parents to make no direct efforts to stop the thumb-sucking. The normal tendency is for the child to give up the habit gradually as he acquires inner security and interest and absorption in the world around him. Efforts to stop the habit from the outside, whether they consist of physical restraints, punishment, nagging, or teasing, seem only to increase the child's need of his thumb. Sometimes a child who has practically given up thumb-sucking does it only when a certain relative is near by who has always made most fuss about it. We all know dozens of cases where every form of physical restraint and moral intimidation were used without beneficial effect. If the parent objects to this "laissez-faire" attitude toward thumb-sucking on the basis that the teeth are being made crooked, the answer again is that letting the child alone is often the quickest way to stop the thumb-sucking and the threat to the teeth.

A physician might summarize his discussion with a mother about weaning and thumb-sucking as follows: "Every baby is born with a strong instinct to

suck. The intensity and duration of this instinct seem to vary in different individuals. We should consult the baby about the time for weaning from the breast or bottle. One infant at 9 months is bored with the bottle, enthusiastic about milk from the cup. He seems ready for gradual weaning. Another at the same age rejects the cup and shows a deep devotion to the bottle. He may not be ready until 15 months or later. Do not force for fear of making him balky or resentful. Urging may prolong his dependence on the bottle. Thumb-sucking in the early months suggests that the infant is not getting sufficient suckling satisfaction at breast or bottle. At the first sign try to prolong the nursing time and to retain frequent feedings. By the age of one year thumb-sucking appears to have become a comforter when the baby is tired, bored, or frustrated. Constructive treatment consists in insuring that his life is as happy as possible, counting on him gradually to give up the habit as fast as he is able. In a persistent case efforts to interfere directly seldom succeed and may prolong the habit."

BOWEL TRAINING

There is a widespread but unfounded belief that good health is acquired through meticulous regularity of bowel movement. In order to get the baby started early on this mythical road to health, and also for the sake of general elegance, it has become the style in our twentieth century American civilization to put a lot of effort into and to take great satisfaction from early and rigorous toilet training. Often to the parents' despair training has broken down at a later stage of the child's development and the child has resisted retraining until an abnormally late age. The psychoanalysts have felt that in certain individuals these over-vigorous training efforts created permanent distortions of the personality.

In the early months of infancy the movement of the bowels is a fairly simple reflex. It is true that when the reflex evacuation occurs at a predictable time of day the assiduous mother can catch the movement in an appropriate vessel. But it is more the mother who is trained than the baby. As the infant gets into the second half of the first year and acquires voluntary control of the lower half of his body, he acquires more voluntary control of the bowel movement too. For instance if the mother rushes him to the potty too abruptly he may become startled and cease pushing. As he gets into the second year he acquires not only further control, but also a genuine interest in the movement as well. He turns around to see what he has done, babbles about it, even plays in it if he has not been inhibited. He gradually takes a possessive proprietary attitude toward it, brings his mother in to admire what he has done.

Each of us has been told by at least one happy-go-lucky mother that her baby trained himself to the toilet in the second half of the second year without her making any effort. The child, naturally, in the course of his social development reaches a stage where he wants to deposit his movement in the same place that the rest of the family use, just the way he wants to use his mother's toothbrush or mop.

Observation of children trained for the bowel movement at different age periods suggests that the age at which the baby is first set on the toilet is not of primary importance. There are babies trained early who stay trained without gross evidence of personality distortion. There are babies trained early who rebel during the second year and suffer tragic changes in character during the prolonged conflict with a severe parent. And among the babies whose training has been postponed until after the age of 12 months some get into

trouble and others do not. It seems to me that the most important factors are *how the mother goes about it and how the baby feels about it during the second year.*

If during the second year when the baby is becoming more possessive of his movement a stern and exacting mother is going at his toileting hammer and tongs, it is clear why a conflict will occur. It is as if the grim mother were saying by her behavior, "It isn't your movement, it is mine. You must produce it for me, when I say, where I say." This seems to offend his sense of proprietorship and arouses the negativism which is his handiest weapon at this period. It doesn't take an outrageously demanding mother to start a conflict during the second year. Many babies at this age get so sensitive about their rights and interests that they rebel against minor degrees of maternal insistence.

There are other factors in toilet rebellion besides the mother's demanding attitude. Of vital importance is the comfortableness of the bowel movement. The baby who has had painfully hard movements on frequent occasions will naturally dread the toilet seat as soon as he learns what is expected of him there. The request, "Now do your duty," when translated by his experience means, "Now hurt yourself." It is no wonder that he resists sitting down, or if sitting, that he procrastinates. I believe that a large proportion of the babies who resist training come from the group who have had painful movements. This puts on the physician the responsibility of carefully preventing or curing all painful constipation throughout the first two years of life.

Another factor of great importance is whether or not the infant is naturally regular. The baby who always moves his bowels within ten minutes after the first meal of the day is practically never a training problem. He moves so quickly and thoughtlessly that there is no reason for his mother to become insistent. It is when the movement occurs without any regular rhythm that the mother is tempted to become overstrenuous and demanding in her efforts to put him on the toilet often and to keep him there for long periods, to use strong disapproval when he fails, and to act as if he had redeemed himself when he succeeds.

There are three common forms that the resistance against training takes. The first is reluctance to sit on the toilet or even to go into the bathroom. The reluctance may be mild and transitory or it may develop into violent rage and terror. Another baby is more subtle and "polite." He may sit down willingly but nothing happens so long as he is on the toilet, whether he is kept there five minutes or fifty. The movement occurs promptly after he has gotten up. Mothers complain, "He seems to have forgotten what he's put there for." But a baby who has been performing well for several months does not forget that easily. There is more indication that he has moved on to a new phase of awareness and resolved to get matters back under his own control. The third form that resistance commonly takes is for the infant to retain his movement not only while he is on the toilet but afterwards, too. He acquires a constipation of purely psychological origin. The retained movement, however, becomes hard and painful to pass. He now has two reasons for withholding.

At this stage the determined mother is apt to use suppositories or enemas. Almost invariably this intensifies his resistance and alarm. A suppository used for two or three days in the first stages of toilet training may not be harmful though some would prefer not to use them even then. But suppositories or enemas after the child has begun to resist training are dangerous in the extreme and should never be recommended.

What does happen to a small child's personality in the course of a long struggle against training? He is first of all made unduly obstinate and hostile. This in itself is an unfortunate influence at such an impressionable age. But worse than the hostility is the insecurity which usually keeps pace with it. The small child cannot consistently defy his mother without becoming uneasy and guilty and this throws his whole personality out of balance. Such is the case when a boy of 4 has developed a compulsion to touch constantly the seat of his pants and then sniff his fingers. He is obsessed with the fear that he has soiled his pants even though he has not actually done so for a couple of years. In less dramatic form it shows up in the little girl who runs crying to her mother every time she gets a speck of earth on her hand. The fear that was impressed on her in the earlier training period has spread to include dirtiness in any form.

One might summarize a sensible discussion with the parent about bowel training as follows: "It is normal for many individuals to move the bowels irregularly. Do not try to change this as long as the movements are comfortably soft. Every child gradually acquires control of his bowel function and becomes willing to dispose of his movement in a way that is locally conventional. You do not need to become concerned about this process. It seems unnatural to do anything before the baby can sit up. It is important to keep his bowel movements soft so that he will not dread defecation. When you begin to put him on the chair or toilet, do it casually and briefly. This means putting him on it at just the right moment, an easy job with the regular baby, but one calling for ingenuity or postponement of the whole program when the movement comes at any time of the day. Do not make it a moral issue. Between 1 and 2 years it is normal for the baby to acquire a proprietary interest and pride in his movement. During this period he may show resistance to your efforts to capture his movement. He may object to going to the bathroom or wait until he gets up to move his bowels, or become constipated. Relax your efforts gracefully until he feels more cooperative. Your persistence, especially if you resort to suppositories or enemas, will only increase his rebellion and distort his personality."

URINE TRAINING

Control of the urinary bladder, like control of the bowels, is something which the child gradually acquires by himself through physiologic development. The most that the parent can accomplish is to persuade the child to void in the conventional receptacle a little earlier than the child would have gotten that idea by himself. During most of the first year the bladder retains little urine and voids frequently though there is considerable variation in different individuals. A great majority of babies do not retain their urine for as long as two hours until they are approximately 15 months old. By this age they have usually acquired enough conscious awareness of urination to comprehend the purpose of toileting if the mother has gone at it in a sensible way. At this period, however, the mother has to take all the responsibility. The child becomes aware of what is about to happen only a few seconds ahead of time and participates voluntarily only to the extent of standing still. During the second half of the second year he shows increasing voluntary control. If his mother has been teaching him that she expects the urine to go into the toilet, he now retains the urine for a few seconds beyond the stage of comfort and may signal his mother with some sound that signifies urgency. He may on the other hand forget to warn her until it is too late. Most children still need to be watched and reminded into at least the first part of the third year.

Night control is not usually acquired until after the child has taken over the responsibility of keeping himself dry during the daytime. But as should be pointed out to parents, retention of urine at night is a normal development in the inherent maturing of bladder function and has little to do with whether the child is picked up during the evening. It is true that a dry bed is secured a little earlier if the long night interval is broken. But the child would not be caught dry, either at 10 P.M. or at 7 A.M., unless the bladder were already tending to longer and longer retention. That it is not the parents' training efforts that make the child dry at night is shown in another way by the rare child, usually a girl, who jumps the gun and becomes dry at night before the age of a year and before her parents have made any move at even daytime training.

What are the causes of delayed control both day and night? First of all there is the apparently wide variation between individuals in the maturing of bladder function as is shown not just by individual cases but by the observation that on the average boys are slower than girls.

Training itself, if it is done in the wrong spirit, sometimes works to postpone voluntary control. The child between 1 and 1½ who is rigorously set down once an hour and kept there for long periods sometimes rebels against this unnatural imprisonment and becomes firmly determined never to void in the proper place. This resistance shows up more often in prolonged night wetting. A 2-year-old son of ambitious parents is at first caught dry about half the time at 10 P.M. and 7 A.M. The eager parents redouble their efforts and pick him up at 9 P.M., midnight, and 6 A.M. At first their zeal is rewarded but after a few weeks of this night work, coupled with exhortations and admonitions during the daytime, he gets wetter and wetter. Instead of being warned by these negative results the parents resolve to torture themselves and the poor child even further and take turns getting him up every two hours right through the night. Again there is partial success at first. But after a while the boy's resistance becomes so ingenious even in his sleep, that he wets before even two hours are up.

At least in some individuals tension and uneasiness of many kinds seem to readily communicated to the bladder, rendering it less capable of relaxing and of retaining urine. It is common for the 2- or 3-year-old who has been dry at night for six months to begin wetting again temporarily when he moves to a new house, or when his mother leaves him to go to the hospital, or when the new baby sister comes home, or when he is frightened by a dog, or after he has gone to the circus. This mechanism is no more mysterious than the frequency of the adult athlete before the race. If almost any kind of emotional disturbance, small as well as great, can cause a child to relapse temporarily into enuresis, it is easy to see why a child who lives in a constant state of tension during his early years never has sufficient equanimity or inner relaxation to become dry in the first place.

When the physician is consulted because a young child is still wetting his bed, the first question should be whether there are tensions operating to postpone the child's normal inherent progress to dryness. In one case the child needs only a little more time to feel at home in a new situation. In another the friction between himself and his parents centers around a feeding problem. More commonly it is apparent that the mother's handling all day long is characterized by pushing, nagging, and unnecessary interference. Occasionally the only problem is that the parents are expecting perfect control at an age when a good proportion of children are still wetting regularly or intermittently. Certainly if the parents are going at the enuresis by intensive methods that are bringing

diminishing returns they should be called off. This is done not with the promise that this new technique will bring immediate success, but that in the long run it will work in the right direction. In the meantime less harm will be done to the child's personality.

The physician is often troubled with the question of whether he should recommend a complete urological examination. There are cases, of course, where the symptomatology or the results of urinalysis demand further investigation. But in a great majority of cases of slow bladder control there is no reason to suspect an organic cause. The point is that hospitalization, anesthesia and instrumentation, with or without pain, are all alarming to small children. This danger should be given serious consideration in deciding whether or not to investigate further.

One might summarize a discussion of urine training with the mother as follows: "Urine training is largely accomplished by the child himself. His bladder function, through a normal process of maturing, comes to retain urine for longer periods. Simultaneously the child acquires a conscious control of voiding. Your baby, if he is average in this respect, will, in the neighborhood of a year and a quarter, begin to retain his urine for about two hours at a time. He will also be wise enough at this stage to see what you are after when you put him on the toilet. If you put him on only when he is dry after two hours, you will insure three things: (1) His bladder function is ready for cooperation. (2) His bladder at that moment will be full. He will urinate soon. Therefore you will not have to antagonize him by keeping him on for a long time. (3) Your training efforts will be gradual since you will only find him dry occasionally at first. After some months he will begin to take the responsibility of telling you when he needs to urinate. In time also his bladder will learn to retain urine throughout the night. Inner security and emotional relaxation are necessary for this progress of bladder function."

ANXIETIES IN THE EARLY YEARS

The fears of children shift with age. The newborn is alarmed by loud noises and loss of support. By about 5 months he can recognize the difference between friends and strangers and may cry with anxiety if approached too suddenly.

By a year babies are apt to show that they now realize that they depend on their mothers for comfort and safety. Mothers often complain at this stage, "He is getting so he cries every time I go out of the room." Usually the child who cries this way is confined in his crib or play pen. The mother hopes to keep him in the pen for many more months because it is practical. Some mothers even think that confining a child by himself will develop his capacity for independence.

It seems to me wiser when the baby has reached the stage where he is no longer happy in his pen and feels lonesome every time his mother leaves the room to admit that he has reached a new phase in his emotional development and to let him out on the floor. When he wants to be near his mother he can creep or toddle after her. Then when his need for security is satisfied he gets the urge to do a little independent exploring and moves into the next room. After ten minutes his hankering for company reasserts itself and he scrambles back to his mother again. By degrees he increases his independence, partly by the very process of satisfying his need for dependence as soon as he feels it. It seems to me fair to say that the baby who is kept crying in his pen while his mother is out

of the room is only becoming more convinced of his own insecurity. If the physician suggests letting the child play on the floor as soon as he becomes unhappy in the pen, the mother will immediately protest that the baby will break things or hurt himself. The answer is that eventually the household furnishings must be rearranged anyway to allow him scope for exploring without too much danger to himself or the bric-a-brac. Why not now when he shows he needs it? He will not be more reasonable at a year and a half.

There is another side to the insecurity which develops around the age of a year. As the infant becomes more conscious of his dependence on his mother he also is apt to become much more suspicious of strangers. In the physician's office a majority of the babies who at 8 or 10 months were quite unafraid, now between 12 and 15 months leap to their feet in alarm as he approaches and try, howling, to climb onto their mothers for safety. The child who between 1 and 2 sees little of anyone besides his parents, tends to retain this suspiciousness both of adults and children. Then when he is thrown among outsiders at 2 or 3 he shrinks back with a look of alarm and tries to hide behind his mother. At best it will take him a long time to learn that other grownups and other children are fun too. Some overprotected children never do learn the joy of give and take even in adulthood.

The baby at 1 year, even though he has an initial timidity about anyone strange, nevertheless has also a great passion to approach, to make friends. This outgoing urge overcomes his caution if he is allowed time. A mother should be encouraged to give her year-old baby plenty of opportunity to get used to outsiders, especially children. Of course he will not develop much capacity for *cooperative* play before the age of 2 but if he learns before 2 that there are other children in the world and how to play in their presence, he will by 2½ be ready for give and take when that phase is due.

There appears to be a new phase of increased dependence that crops out between the ages of one and three quarters and two and a quarter. Mothers often complain at this stage that their children are getting more tied to their apron strings and shy with strangers, showing reluctance to being left alone at bedtime, sometimes calling out or climbing out of the crib and joining the family a dozen times during the evening. Some of the children who start nursery school before the age of 2½ cry at first when their mothers leave them there and take a longer time to feel at home with the group. This tendency to greater dependence around 2 makes the child more sensitive to any sudden or prolonged separation from the mother or other close adult. This should be taken into consideration if the mother is thinking for example of taking a job, going on a trip, or having an elective operation. If the right preparations are not made her absence may create a real anxiety state in the child, particularly if he is an only child or already overdependent.

Here is a typical story of a badly handled separation: A mother abruptly takes a job leaving her 22-month-old boy in the care of a woman with whom he is not familiar. The first day he is well behaved but when his mother returns that evening he hangs on to her like a leech, refusing to let the other woman come anywhere near. The next morning there is a scene when his mother leaves and in the evening he not only refuses to let her out of his sight but also he refuses to be put in bed. If she tears herself away he may cry anxiously for hours. If she sits by his crib he lies down only as long as she sits still. Her slightest move toward the door brings him instantly to his feet crying.

Anxiety about wetting often seems to play a part in these cases. The child keeps begging to be taken to the toilet throughout the evening or when he

wakes later. One is apt to jump to the conclusion that he is using this merely as an excuse to hold the parents near but it probably has another significance too. It is when the child is about 2 that the adults are apt to express definite concern about having him stay dry. It may be that his fear that he will displease his mother by wetting gets linked up with his fear that she will go away and leave him again. Once an anxiety over separation from the parent is started it is difficult to allay. Letting the child "cry it out" may take months, is agonizing to the mother, and probably further destroys the child's security. The only solution I know of for the severe bedtime anxiety, and it is not an easy one, is to have the mother settle down beside the crib until the child is *surely* asleep, even if it takes hours at first, and to count on his slowly returning confidence to shorten his anxious, wakeful period by gradual steps.

I think that such anxieties can be largely avoided if the emotional dependence of young children is understood and respected. This brings up the whole subject of parental, foster parental, and group care. (In this discussion age divisions are used arbitrarily for simplification.) In the first place mothers should understand clearly that the young child, particularly up to the age of 3, derives his greatest security from a sense of belonging intimately and irrevocably to his parents. Generally speaking a mother should be discouraged from going to work during the child's early years unless it is really essential from the point of view of finances or of the mother's morale, and unless there is a relative, maid, friend, or foster mother to take her place who is familiar, loving, comfortable and can be counted on to last at the job, or unless there is excellent nursery school care to which the child is mature enough to adjust.

If the mother must leave him in the care of a stranger coming into the home the important thing is to accustom him to her, to transfer his dependence to her by gradual degrees especially if he is in the sensitive period around 2 years. Ideally he should have a chance to get used to the stranger's presence before she even tries to do things for him which itself may take a couple of weeks or more. Then gradually she participates in his care. When he accepts this his mother can begin to leave him first for only half an hour, then lengthening her absences as the child adjusts to them. Many children stay secure without these precautions which may seem overfussy but I think they are worth while in order to avoid the occasionally bad outcome.

Needless to say the person to whom the child is to be entrusted should be chosen not primarily on the basis of experience, training, or cultural level but for qualities that are vital to the child: a capacity to love him warmly without smothering him, to handle him easily without nagging or severity.

It is wise I believe to avoid the usual type of *day nursery* care, certainly before the age of 2 or 2½ years. In the first place it is doubtful whether any child before 2 can get enough sense of being really cherished from ten or twelve hours a day of *group* care of even the best quality. Furthermore few day nurseries have staffs of teachers trained in modern concepts of children's needs.

On the other hand, first rate *nursery schools,* well equipped and with a sufficient number of trained teachers selected on the basis of temperament and understanding, have a contribution to offer the 2- to 6-year-old children of working or nonworking mothers. They supplement the modern child's life where it is most often lacking—in play space, in variety of toys and apparatus and materials, in companions of the right age, in opportunity to learn the fun of cooperative play and to lose self-consciousness and overawareness of parents. Here for a few hours (three to four) a day the child may gain much but it is

important to accustom the child under 3 to nursery school gradually. If the teachers are understanding and know their job, they will encourage the mother of a sensitive younger child to remain at school for part of the day and then take him home herself for a sufficient number of days until he comes to feel at home and gradually shifts some of his dependence to the teachers. The commonest mistake is for the mother to try to sneak away on the first or second day just as soon as the child is half absorbed. When he discovers her absence he feels abandoned.

The ideal arrangement is when school runs for half or three quarters of the day, leaving a number of hours when the child can be with his mother. All-day nursery schools may be necessary where mothers have to take full-time jobs but this long separation is less desirable, especially for the child under 3. Practically all children benefit from first-rate nursery school care by the age of 2½, and most do so by 2. There is an occasional child of 2 who is so intensely dependent that he cannot tolerate the separation from mother or the immersion in the group even when it is gently done. He requires a more gradual weaning: a slow familiarization with one or two playmates in the mother's presence and a few more months of maturing. If his mother must work he may do better until he is 3 with an excellent foster mother. The baby or small child up to 2, 2½, or 3, who *must* be left *outside* the home with strangers for all-day care, may better be placed in a private home ("foster care" or "foster day care") that is supervised by a conscientious agency in the care of a proved, motherly woman who is able to give one or two young children the kind of attention and affection that approximates the mother's own. The mother and child should together visit the foster mother until confidence in her is built up.

The anxieties that a child is liable to have by the time he is 3 or 3½ are more complex. He may acquire a sudden fear of dogs without ever having been attacked by one. He hears that someone has died and after a few questions about what death is asks anxiously, "Do I have to die?" The sight of a cripple fills him with dread. He has reached a stage of mental and emotional development where he can imagine and apply to himself dangers which he has never experienced.

These fears appear to develop more often and more intensely in children who in their earlier period have been overprotected or who have been made tense by struggles over such matters as feeding or toilet training. It is as though what previously had been a vague inner uneasiness is now able to be crystallized by the imagination into a specific phobia. If this is all true then the prophylaxis of fears at 3 consists in the wise handling of a child from birth on.

There are further possibilities of prevention in one particular group of fears. The 3-year-old is not only alarmed by truly crippled and malformed people. His limited experience and fertile imagination sometimes make him misinterpret the natural physical differences between boy and girl and jump to the conclusion that some injury has befallen the girl. This misunderstanding worries girls as well as boys, and in both leads at times to a preoccupied, anxious handling of the genitalia.

It is important for parents to know that questions about bodily differences occur to children around the age of 3 and to answer the first questions cheerfully, reassuringly, making it clear that girls are *meant* to be one way and boys another. If the parent tries to hush the question it will confirm the child in his suspicion that something terrible has happened. The little girl needs extra reassurance because at her age it seems better to have something, whether she was

intended to have it or not and this is a good time to tell her that girls can have babies of their own when they grow up.

If physicians realize that worry about bodily differences is a common cause of preoccupied handling of the genitals in early childhood, they can then not only give helpful constructive advice to parents but they will recognize also the importance of refraining, when possible, from operations or treatment in the genital region. It has been traditional to blame masturbation on local irritation and to recommend circumcision for the boy or vaginal treatments for the girl who has evidence of mild inflammation. Handling of the genitals itself often produces mild infection but this is effect rather than cause. If the child is doing it because of worry that some injury has happened or may happen, then the worst possible treatment is actually to operate. What the child is dreading comes true. It is clear also why the parent should not attempt to combat the masturbation with threats that it will cause injury. Many modern parents, having heard that it is considered wrong to make a moral issue of masturbation, slip into the alternative of telling the child that the practice will hurt his genitals. With this new reinforcement of his fear he may cease handling himself. But the psychological effect is bad and may result in sexual maladjustment later. The parents' efforts should be directed to understanding why the child masturbates, to reassuring him about his anatomy and to making his daily life satisfying and absorbing. It is better to say nothing to the child about the masturbation. But if they feel that they must say something at least to stop his masturbating in public, let them confine themselves to some remark such as, "People don't think it is very polite."

To summarize then: It is helpful for physicians and parents to know that children become liable to characteristic anxieties at different ages. These are by-products of various stages of emotional development. The baby around a year is becoming aware of his dependence on his mother. His increasing interest in things around him will wean him of this if he is spared too much parental concern or domination and is allowed freedom and contact with other adults and children. His need of his mother acquires a new intensity at about the age of 2 years. Abrupt unprepared separation from her way precipitate an anxiety state. Mothers should be discouraged from going to work when their children are young unless the need is imperative and unless the child can be left with an ideal and familiar substitute either in the home or in a foster day home. *All-day group* (nursery) care before the age of 2½ is generally unsatisfactory. First-rate nursery schools have much to contribute but because of the greater dependence of children up to 2½ or 3, their introduction should be gradual and all-day attendance should preferably be avoided.

The 3-year-old's imagination makes him apply all kinds of real and fantastic dangers to himself. Anxiety about his genitals is common and often leads to preoccupied handling. This calls for understanding and wisdom on the part of parents and physician.

JEALOUSY OF THE NEW BABY

Many severe behavior problems spring from a corrosive jealousy of a new baby in the family. The jealousy is more apt to be intense when the older child is under 5 years of age. This is the period of his life before he has formed strong attachments and interests outside the home, when his main security comes from his close emotional dependence on his parents. There is also a greater likelihood of severe jealousy when the older child is the first in the family. He has been the recipient of all the adoration and fussing of which

his parents are capable. He has taken this attention for granted and tacitly assumed through no fault of his own that he was the center of the universe. The impact of the arrival of a competitor may be shattering. One child becomes aggressive and vengeful; another loses all his joy in life and mopes disconsolately for months. Even when the child eventually makes good progress in digesting his jealousy, his personality throughout the rest of childhood and adult life is apt to show sensitive spots from the old hurt.

Jealousy is one of the facts of life and cannot be wholly prevented by any bag of tricks. Most depends, of course, on the wholeheartedness of the parents' love for each of their children. Advice from a physician cannot make up for defects in the parents' attitudes. But the physician should do what he can both by practical suggestions and, more important, by so interpreting the older child's predicament that the parents, sympathizing, will handle the situation with a maximum of understanding.

It is better for the child to know ahead of time that a baby is expected so that he can get used to the idea gradually. This helps less than an adult would expect because the small child's imagination may not create anything like the reality. He may visualize an animated doll to tote around or a full-fledged companion. Even if he knows and loves a neighbor's baby, he is apt to find that his mother's baby evokes entirely different feelings. Most professionals in the children's field feel that the child should know that the baby is growing within the mother's abdomen. This is not primarily for the sake of abstract honesty but because it is known that many children beyond the age of 3 and some under 3, suspect the truth anyway, through a combination of shrewd observation, slips in the conversation of adults, and perhaps a touch of intuition. One supposedly innocent 3-year-old will call attention to this mother's changing girth with hints, partly questioning, partly accusatory. Another will suddenly hit at her abdomen as if already jealous of what he suspects is there. The child who is hesitantly coming to his own conclusion that the new baby is growing in the mother is likely to become troubled. It is not that he cannot take the truth. What worries him is his mother's evasion in continuing to talk about the stork theory or the hospital theory in an unconvincing tone when he is pretty sure the baby is coming from elsewhere. Many parents refrain from telling the child the truth for fear that it will open the door to other embarrassing questions. This is an unjustified fear. The child before the age of 6 years will not put his parents on the spot to explain conception. The likely question will be, "How did the baby get in there?" to which at this age the most understandable answer is that the baby grew from a seed which was there all the time. To the question, "How will it get out?" the answer might be, "Through a special place." Incidentally, parents should be warned against predicting the sex of the baby ahead of time since a wrong guess may lead to long-lasting disappointment.

Some mechanical readjustments in the household are usually necessitated by the arrival of a baby. Wherever possible these should be made several months before the baby's birth and presented to the older child as evidence or growing up. If he is to move into another room or into a big bed, he should graduate to them because he is a big boy and not be dispossessed by the rival in person. If he is to enter a nursery school he should become well established there before his mother's confinement. Then when the baby arrives, even though the older child feels somewhat slighted at home, his satisfying life at nursery school will

help to ease the pain. If he is sent off to nursery school after the baby's arrival, he may resent it as banishment, resist going, resist fitting in.

It is vital, particularly when the older child is in the neighborhood of 2 years, that he feel comfortable and secure with the adult who will care for him while his mother is in the hospital. If a relative or maid is coming into his home, she should either be someone whom he knows well and loves, or she should come two or more weeks ahead of time and take over his care gradually. When a very young child is abruptly left in the care of a stranger, he may behave well while his mother is away, but when she returns all his latent anxiety suddenly comes to the surface. Such a state may last for many months and make even more difficult his other problem of adjusting to the baby.

First impressions are most important. When a mother and father bring the new baby home from the hospital there is usually a great deal of hectic confusion for at least an hour. The older child is lost in the shuffle. No one has time to fuss over him and he stands by, looking wretched. If possible he should be off on an excursion during this time and come home when his mother is able to take him in her arms and give him her undivided attention.

Now that the baby is at home what are the parents' cues? The first principle is to play down the importance of the baby. This means talking about him as little as possible, enthusing over him as little as possible, taking care of him casually when the older child is around. The hardest thing for many children to take is seeing the baby nursed, especially when this is at the breast. Often the older child will want a bottle, too, and it is a wise mother who cheerfully provides it. If this is well handled the child will not repeat the request often since he finds that the bottle is not really a delight.

Even though one advises the mother to feed and care for the baby as much as is practical when the older child is preoccupied with other activities, she should, of course, be equally warned against shutting him out of the nursery whenever he has the desire to see what is going on there. If there is a relative or nurse helping out in the early weeks, it is usually best to have this person taking care of the baby, allowing the mother to give as much attention to the older child as she used to.

Then there are the other relatives. When the father comes home from work he should resist the natural impulse to greet the older child in the front hall with the question, "How's the baby been today?" but should stop to play with him for a while before he drifts in to see the newborn. When Aunt Nellie telephones to arrange a visit to the baby, the mother can remind her that the older child is still counting on being her favorite and will appreciate a present much more than the baby will.

So often Aunt Nellie in her thoughtless enthusiasm greets the older child with the breathless question, "Where's that darling baby sister of yours? I have brought her a present." For these situations the mother might have a box of ten-cent store toys from which to produce a gift each time one arrives for the baby.

Many parents have already heard of the value of letting the child share in the ownership and care of the infant. It is fine for the older child to bring the bottle from the icebox or the towel to the bath provided he enjoys this work and does it spontaneously. Another child will overcome the feeling of being an outsider by an elaborate care of her doll which follows her mother's care of the baby to the last detail.

It will help the parents to know what different forms jealousy may take. Everyone knows what it means when a child grabs a heavy object and whacks the baby over the head with it. But many mothers think it is clumsiness when the child hugs the baby with an embrace which begins gently and ends with a grip which brings a squawk from the infant. One child turns all his resentment against his mother and grimly empties the flowerpots on the living room rug. Another loses all joy in his usual pursuits and follows his mother from room to room sadly sucking his thumb. Children frequently revert to wetting by night and by day and some even soil themselves, for which there are several explanations. There is the element of defiance. There is the desire to receive the same tender care by imitating the baby. But it must also be realized that any severe unhappiness, without the elements of resentment or imitation may lead to a dramatic regression to infantile behavior.

The mistake is sometimes made of thinking that because a child shows affection for the baby there is no possibility of jealousy. There is always some latent jealousy to be guarded against even when all is love on the surface. And the child who has shown nothing but hatred for the baby at home may defend him like a lion outdoors if a stranger approaches. It must also be remembered that a child may show wholehearted delight in the baby for months until the day when the baby snatches one of his toys.

It is generally believed by psychiatrists that a strong destructive instinct like jealousy will be better coped with if it is allowed to stay near the surface. It will do more harm to the personality and persist longer if it is deeply repressed from the outset. What is a mother to do then, when her child make a cruel attack on the baby? The common impulse is to shame the child, to overwhelm him with a feeling of guilt. If such a maneuver succeeds too well, the child, dreading the intense disapproval of his parents, will not dare to show or even let himself feel his jealousy. The emotion, however, is not dissipated but only driven underground. A case in point is that of a 2½-year-old girl who for months after the birth of a baby sister wandered around in a sort of daze. She entered into no games herself but only watched the other children in a preoccupied way. When she saw a small boy riding a tricycle she would murmur, "Susy (her baby sister) has a bike." When a dog passed she murmured, "Susy has a dog." She was obsessed with Susy and objects in the world around her served only to remind her quite illogically of the baby.

If it is unwise for the parent to shame the child, to scare him out of expressing his jealousy, what is she to do when the child makes a physical attack on the infant? She has to jump in and use physical restraint, but she can turn the restraint into a hug and say to the child comfortingly, "I know how you feel sometimes. You wish there were no baby here at all. I love you just the same." This tends to reassure him and lessen his jealousy. For jealousy is not just hatred of the baby. It is hatred of the baby for fear he will monopolize the parents' love. If the parents can be helped to put themselves in the child's position they will begin to see that his cruelty and mischievousness are not simply matters of impoliteness or cussedness but are reactions to severe anxiety.

There are three further points which may seem partly to contradict what has been said before. First, some conscientious parents become so fearful of causing jealousy that they feel positively guilty about having produced a new baby at all, develop an uneasy apologetic manner toward the older child and fall all over themselves trying to appease him. This attitude does no one any good

and specifically convinces the child that his parents have done him wrong. The parents' cue is tact, not abjectness. Second, the new baby will of course need an increasing share of attention and affection and acceptance as his waking hours increase. The older child should be increasingly able to tolerate this if a good start has been made. Finally, jealousy is not entirely a destructive experience. Probably everyone has to go through a certain amount of it. If it is not too bitter and is solved constructively, the result should be a more resilient, adaptable, tolerant personality.

REFERENCES

1. Davis, Clara M.: Am. J. Dis. Child. 36: 651, 1928.
2. Levy, David M.: Am. J. Orthopsychiat. 4: 203, 1934.

Erratum

In the article by Taran and Jacobs entitled "Salicylate Therapy in Rheumatic Fever in Children" in the July, 1945, issue of the JOURNAL, on page 60, line 25, the sentence should read as follows: "The total dose of sodium salicylate was calculated for each child on the basis of 1½ grains per pound of body weight and the equivalent amount of the 1 per cent solution was given intravenously by the drop method to be administered in a period of six hours."

American Academy of Pediatrics

Proceedings

Report of the Treasurer

STATEMENT OF RECEIPTS AND DISBURSEMENTS

JULY 1, 1944, TO JUNE 30, 1945

Balance in checking account, July 1, 1944			$ 5,810.69
Balance in savings account—State Bank & Trust Company			2,559.98
Balance in Savings account—First National Bank & Trust Co.			1,510.06
			$ 9,880.73
Receipts:			
Dues		$26,728.00	
Exhibits, 1944 Meeting		2,567.50	
Initiation fees		3,249.06	
Interest earned		874.64	
Pamphlets—Child Health Record	$475.24		
Immunization Procedures	993.33		
Vitamins	12.80	1,481.37	
Subscriptions, Men in Service		717.50	
Wartime assessment (1945-1946)		5.00	35,623.07
			$45,503.80
Disbursements:			
Annual Meeting—1944		3,879.40	
Bank charge and exchange		92.73	
Bonds		2,000.00	
Certificates and mounting		52.42	
Executive Board		2,763.66	
Miscellaneous		261.17	
Office supplies and equipment		280.27	
Postage		639.10	
Refunds, initiation fees		150.00	
Rent		2,441.32	
Salaries—Secretary	$7,500.00		
Assistant Secretary	600.00		
Stenographer	2,235.00		
Office	1,563.22	11,898.22	
Stationery and printing		1,460.43	
Subscriptions		7,275.35	
Telephone and telegrams		397.50	
Travel expense—Secretary		307.28	
Treasurer's bonds		92.50	
Expense—Regions	2,692.47		
States	134.92		
Committees	1,271.97	4,099.36	
Pamphlets—Child Health Record	304.59		
Immunization Procedures	1,380.37		
Vitamins	.47	1,685.43	39,776.14
Balance, June 30, 1945			$ 5,727.66
Balance in checking account, June 30, 1945			$ 344.33
Balance in savings account—State Bank & Trust Company			3,838.72
Balance in savings account—First National Bank & Trust Co.			1,544.61
			$ 5,727.66

The Social Aspects of Medicine

THE PROGRAM FOR MEDICAL CARE OF THE MEDICAL INDIGENT IN THE COUNTIES OF MARYLAND* WHICH HAS BEEN ENDORSED BY THE MEDICAL AND CHIRURGICAL FACULTY OF MARYLAND

DEAN ROBERTS, M.D.

The Medical and Chirurgical Faculty of Maryland, aware of many deficiencies in the present status of medical care in this State and of the absence, in Maryland, of an official warrant for any group to evolve a coordinated program of medical care, proposed on August 23, 1939, in an open letter to the Chairman of the Maryland State Planning Commission that a standing committee of the Commission be formed to survey the problems of medical care for the citizens of the State. It was suggested that this Committee should formulate, from time to time, recommendations for the extension and better utilization of existing medical facilities, and for the development of such new facilities as required. The Faculty recommended that this Committee be composed of representatives from all agencies concerned with the various aspects of medical care as well as from the general public.

In response to this letter from the Medical and Chirurgical Faculty of Maryland, the State Planning Commission, with the approval of Governor Herbert R. O'Conor, appointed a standing Committee of the Maryland State Planning Commission, and designated Maurice C. Pincoffs, M.D., as its Chairman. The Committee was composed of thirty-four members, the majority of whom were physicians, but also included representatives of the dental profession, nursing profession, hospitals, City and State Health and Welfare Departments, pharmacists, labor, and the lay public.

The Committee held its first meeting on January 23, 1940, and Abel Wolman, Dr. Eng., Chairman of the Maryland State Planning Commission, charged the Committee with the task of determining the existing defects, if any, in the present private and public facilities for medical care. If deficiencies were found, the Committee was expected to determine and evaluate their amount and character. Furthermore, the Committee was to suggest the necessary corrective measures, to indicate what costs were involved in such a program of correction, at what rate such changes might be introduced, and the most logical source of funds.

On February 1, 1941, the survey staff was organized with W. Ross Cameron, M.D., in charge. Dr. Cameron was assigned by the State Department of Health to act as Director of the Survey. Original plans called for a survey period of approxiamtely fifteen months.

About July 1, 1941, world conditions were such that war seemed imminent. Since several members of the Committee expected to be called into active service momentarily, it was decided to curtail the field survey, and to interview representative groups of physicians in three sections of the State rather than to interview all physicians.

Dr. Pincoffs, Chairman of the Committee volunteered for active service with the U. S. Medical Corps, and was succeeded as Chairman by Allen W. Freeman, M.D., on April 1, 1942. A few months later Dr. Freeman retired from active participation due to illness, and was succeeded by Dr. Victor F. Cullen, M.D., who served as Chairman for the duration of the study.

THE FIELD SURVEY

The objectives of the survey were as follows:

1. A study of certain characteristics of the population.
2. A description of medical care facilities including:
   (a) The distribution of physicians, nurses, and dentists, and types of service rendered by each.
   (b) The function of hospitals, health and welfare departments.
   (c) The activities of other governmental, voluntary and private agencies.
3. Estimates of the number of indigent and medically indigent, and procedures followed by such individuals in securing medical care.

*The City of Baltimore is excluded.

4. A study of the health needs with suggestions for securing more effective use of existing agencies either by improving or extending their activities, or by the organization of other services.
5. Estimates of the cost of such a program.

In obtaining the information called for in the survey, the president or secretary of every County Medical Society was interviewed, and all physicians in seven counties, with others selected at random from widely separated areas. The eighteen general hospitals in the counties of Maryland were inspected and hospital facilities tabulated. The County Health Officers, and the executives of the twenty-three County Welfare Boards were interviewed, as well as directors of State Departments of Health and Welfare. Opinions on the need for providing medical care for the indigent and medically indigent were also obtained from many citizens from all economic levels.

In April, 1944, the report of the Committee was published.* In this report the Committee on Medical Care recommended that a program providing medical care for the indigent and medically indigent in the Counties be established, and that this program be formulated and administered by the State Department of Health, who would be responsible for the compensation of physicians and of institutions for services rendered to eligible persons.

It was recommended that a Council on Medical Care be established which would act in an advisory capacity to the State Board of Health in the development and administration of the program, to be constituted as follows:

Two members appointed by the Council of the Medical and Chirurgical Faculty of Maryland.

Two members appointed by the State Board of Health, one of whom must be the Director of the State Department of Health.

One member from the Faculty of the Medical School of Johns Hopkins University, and one from the Faculty of the Medical School of the University of Maryland, to be appointed by the governing body of the respective medical schools.

One Maryland hospital administrator appointed by the Maryland-District of Columbia Hospital Association.

The Director of the State Department of Welfare.

One dentist appointed by the governing body of the Maryland Dental Association.

One nurse appointed by the Board of Directors of Maryland State Nurses Association.

The Commissioner of Mental Hygiene.

The Superintendent of the Tuberculosis Sanatoria of Maryland.

One member appointed by the Executive Board of the Maryland Medical Association. (State organization of Negro physicians.)

For the administration of the Medical Care Program, it was recommended that a Bureau of Medical Care be established in the State Department of Health. It was also recommended that County Health Officers, in cooperation with the Medical Societies, administer the local aspects of the program.

The report of the Committee on Medical Care was presented to the Medical and Chirurgical Faculty at its regular annual meeting in 1944 and was adopted unanimously. The report was then forwarded to the Governor with the request that suitable legislation be enacted to implement the recommendations. A bill to this effect was drawn up and became a law when the Governor signed it on February 9, 1945.

An appropriation of $200,000 per year for two years was made, and although this was considerably less than the estimated cost of the program, it was felt that it would be sufficient for a beginning, bearing in mind the high state of prosperity of the nation.

DEVELOPMENT OF PLANS FOR MEDICAL CARE

The Council on Medical Care was appointed as provided for in the law, and held its first meeting on May 24, 1945. The Council felt that it was very important that statewide policies be flexible, and that the program be adapted to the most pressing local needs in each county. They, therefore, recommended the appointment of a County Advisory Committee on Medical Care in each county, to be composed of:

Three members to be named by the County Medical Society: One member to be named by the Dental Society having jurisdiction in the county; one member appointed by the Mary-

*"Medical Care in the Counties of Maryland," Publication No. 40 Maryland State Planning Commission, 301 Latrobe Hall, The Johns Hopkins University, Baltimore 18, Maryland.

land Pharmaceutical Association; the Executive of the County Welfare Board; Chairman of the Board of County Commissioners or his delegated representative; the County Health Officer who is to serve as chairman; the counties were given the option of adding additional members to the Committee.

Funds available for the program were allocated among the counties on the basis of the number on relief. County Committees were then charged with the responsibility of making recommendations to the Council as to the eligibility requirements, scope of services to be offered, and fees to be paid. As these reports were received, it became clear that in many counties there were several agencies already in the field of providing medical care, and that there was great need for coordination and unification of Medical Care facilities. One of the basic principles adopted for the Medical Care Program is that it may supplement services or initiate new services, but should not replace existing services.

Based on the reports from the counties, the Council recommended general policies for the program which were subsequently adopted by the State Board of Health. These policies provided that before services start, each county submits a plan, accurately and completely defined to the Bureau of Medical Services. On approval of this plan, services in a given county are begun.

ELIGIBILITY FOR SERVICES

For the first few months eligibility is limited to the recipients of public assistance, except in cases of emergency need of medical care, in which case the Health Officer may authorize care of medically indigent cases. The program will be widened to include individuals who are not on relief, as soon as a satisfactory "measuring stick" can be developed, by which to judge eligibility of this group. Final responsibility for certification of eligibility rests with the County Health Officer.

SERVICES INCLUDED IN COUNTY PROGRAMS

Counties determine the scope of the local program within a wide list of services which includes home and office care, surgery, obstetrical services, consultation, dental care, bedside nursing care, drugs, laboratory services, and clinics in specialty fields. Each county chooses those services for which there are most urgent local needs, and which can be purchased with the funds allotted to the county.

FEE SCHEDULE

In the interest of administrative simplicity, it was found necessary to adopt a uniform fee schedule for all counties. This fee schedule which is given below is based largely on the recommendations made by County Committees.

Home Visits—day (8:00 A.M. to 8:00 P.M.)	$ 3.00
Home Visits—night (8:00 P.M. to 8:00 A.M.)	$ 4.00
Note: If physician treats more than one patient on a home visit, he shall receive the regular fee for the first patient, and $1.00 for each additional patient.	
Office Visits	
Note: No payment allowed for telephone calls	$ 2.00
Hospital Visits—on medical case	$ 2.00
Travel—For home calls more than ten miles from the office of the physician, an additional payment of $1.00 will be made.	
Drugs—Fees for visits indicated above include payment for simple drugs customarily dispensed by the physician. If special drugs of a more expensive nature are indicated, a prescription may be written, and payment will be made direct to the pharmacist. If the physician finds it necessary to dispense drugs, the cost of which is greater than 50 cents, he may enter the cost of the drug on his Medical Report in the space marked "Special Services," and additional payment to cover will be made. Physicians are urged to avoid the use of proprietary remedies when drugs listed in the U. S. Pharmacopoeia or National Formulary can be used.	
Maternity Care—Including prenatal care, delivery and postpartum care. Physician may refer patient to Health Department Clinic for prenatal and postpartum care if he so desires. Note: The law makes no provision for payments to a midwife.	$35.00
Major Surgery—Including preoperative and postoperative care not to exceed	$50.00

Minor Surgery—Including preoperative and postoperative care (simple fractures, dilatation, curettage, etc.) not to exceed	$25.00
Assistant at Major Operation—not to exceed	$10.00
Anesthetist—For general anesthetic—not to exceed	$10.00
Consultation—By local consultant	$ 5.00
By out-of-town specialist (Member of Specialty Board)	$10.00
Note: Mileage for out-of-town specialist will be allowed at 30 cents a mile one way, up to a maximum of $10.00	
Dental Care—Single extractions—not to exceed	$ 2.00
Multiple extractions for same patient at same sitting—first tooth	$ 2.00
Each additional tooth	$ 1.00
Maximum payment for extractions for one patient	$10.00
Silver amalgam fillings, each	$2.00 to $ 3.00
Silicate, or other cement fillings	$ 2.00
Dental x-ray, each	$ 1.00
Maximum fee for dental x-ray on one patient	$ 5.00
Other office treatment	$ 2.00
Full dentures—to be made of vulcanite only:	
Upper or lower denture—not to exceed	$35.00
Upper and lower dentures—not to exceed	$60.00
Repair of denture—not to exceed	$ 6.00
Home visits when essential—same basis as physicians	
Oral surgery—same basis as physicians	
Laboratory Services—In any program providing medical care, indicated laboratory services, including x-ray should be available. When there are existing free services they should be used. Physicians taking x-rays in their offices may be reimbursed at cost, not to exceed a maximum of $5.00 per patient. X-ray or other special laboratory services may be purchased from hospitals or private laboratories on a basis of minimum rates for indigent patients.	

PAYMENTS PRORATED

It was necessary to develop some procedure by which expenditures would be limited to funds available. The only practical procedure available was to set up the amounts available to each county in monthly amounts, and if the total bills from a given county exceeds the funds available for that county, payments are prorated on the basis of funds available. For example, if funds available for a given month in a county totals $1,000, and bills received for that month total $1,500, then payments to physicians would be on the basis of two-thirds of the amount earned. This policy is not considered to be entirely satisfactory, but it is the only practical procedure available by which expenditures may be kept within the limitations of funds available.

ADMINISTRATIVE PROCEDURE

Each month physicians and dentists will submit a single report of services rendered to each patient to the County Health Officer. This report will be reviewed and approved by the County Health Officer, and forwarded to the Bureau of Medical Services from which payment will be issued. If the Health Officer has any question regarding the accuracy or validity of the report he may obtain the advice of the County Advisory Committee. Likewise, if a physician is dissatisfied with payments received he may present his case to the County Committee. If the patient needs bedside nursing care, consultation, or special diagnostic procedures these may be requested by the attending physician, and will be authorized to the extent that facilities are available.

SUMMARY OF THE MEDICAL CARE PROGRAM

The Medical Care Program represents an effort of the medical and dental professions in Maryland to work out with the State and local government a program that will bring adequate medical care to those who cannot afford to pay for it. By offering consultation service, clinics in specialty fields, diagnostic laboratory services, and bedside nursing care, it is felt that the quality of medical care for the indigent and medically indigent can be greatly improved. The program is not limited to any particular age group of the population. The majority of patients will be relief clients, about one-third of whom are children receiving

assistance through the relief categories, Aid to Dependent Children, and Foster Home Care. Policies for the program have been developed with the full cooperation of State and local professional groups. The success of the program will depend largely on the continued cooperation between those administering the program, and those providing services, with full consideration of the needs of the recipients of the program. It is anticipated that errors will be made, but it is believed that these can be promptly corrected as they come to light. This program offers a valuable opportunity to devise techniques of bringing adequate medical care to those who cannot afford to pay for it without changing the basic pattern of medical care under which the science of medicine has made such great progress in recent years.

Madison, Connecticut
August 8, 1945

Dr. Edwards A. Park,
Johns Hopkins Hospital,
Baltimore, Md.

Dear Dr. Park:

The announcement in your letter of recent date that the JOURNAL OF PEDIATRICS was about to initiate a section devoted to the "Social Aspects of Pediatrics" under your editorship will be received with interest on the part of all members of the Academy. The importance of this subject needs no emphasis, both from the standpoint of promoting interest in the participation of our Fellows in the social endeavors of pediatrics to secure and extend the highest quality of medical care for the children of America, but from that of protecting the interests of the science of pediatrics and of pediatricians, the advances of the former together with the widespread cooperation of the latter having been largely, if not solely, responsible for the attainment of better child care in the United States with its resultant lessening of morbidity and mortality among the young.

The premise may be taken for granted that pediatrics has led the van in striving for the extension of preventive medicine as applied to children and in the application of health supervision and immunization against disease through purely altruistic motives. Furthermore, because of the humane and charitable instincts which characterize pediatricians they have constantly labored for the extension of such measures to the less fortunate through the establishment of clinics and health stations throughout the land.

There can be no doubt but that your new column will prove an interesting forum for the expression of opinion of our membership on the various aspects of participation by pediatricians in the social side of medicine which of late has been a topic uppermost in the minds of physicians and the public alike.

There has been during recent years an alarming encroachment upon the rights and prerogatives of physicians on the part of governmental agencies under the guise of social betterment which threaten to undermine the principles which have made medicine in the United States what it is today. No greater threat to the existence of pediatrics can be imagined than the enactment of Federal legislation such as is proposed in the bill recently introduced in the Congress by Senator Claude Pepper who in his press release of July 26 has actually assumed, or at least implied, that his proposed legislation has the endorsement of the Academy of Pediatrics, an assumption which has no basis in fact.

Should Federal and State agencies without consultation and advice from the actual purveyors of medical care promulgate laws which confiscate the intellectual abilities of physicians who alone can distribute such care, with no restriction whatsoever as to the economic need of the beneficiaries? The writer thinks not.

Why should government object to a "means test" in its distribution of medical doles when the very life of government is derived from revenues secured through the "means test" of the income tax? The assumption that Congress objects to such a test in Federal grants is entirely unwarranted as the record will show. In Federal grants for the support of day nurseries for children of working mothers a sliding scale, based upon the means test of wages received by parents, was recognized by government and fees for nursery care established accordingly. Why should such recognition of financial status be accorded the well child and not the sick?

In conclusion, the writer would object vigorously to the indiscriminate extension of free medical services "to all who elect to participate in the benefits of the program," which is the phrase carried in the press release of Senator Pepper explaining the purpose of the bill just introduced.

The charitable concern in the less fortunate and a realization of the humanities, which are attributes singularly possessed by the pediatrician, brought upon him the responsibility of initiating, conducting and promoting the extension of child clinics and health conferences. Federal, State and municipal participation in such welfare activities was of later origin but now threatens to engulf the whole.

Have we pediatricians unwittingly builded a Frankenstein which now threatens to rise up and destroy us and the specialty of pediatrics to which we are devoted?

With best personal regards,
Sincerely,
(Signed) Joseph S. Wall

Joseph S. Wall, M.D., President,
American Academy of Pediatrics

News and Notes

Study of Seven Million Births Showing Child-Spacing Need

From a study of the live births and stillbirths of more than 7,000,000 American babies in the five years from 1937 to 1941 has come important evidence in support of the child-spacing theory. Dr. Jacob Yerushalmy, principal statistician in the United States Public Health Service, has found that the amount of time between pregnancies has an important relationship to the possibility that reproduction will end in the tragedy of a stillbirth. More than 75,000 American babies are lost each year through stillbirths. Precisely how long the average space between births should be to reduce the danger of stillbirth to a minimum, Dr. Yerushalmy was unable to indicate from his findings. He did conclude, however, that "relatively short intervals (between pregnancies) and relatively long intervals are associated with higher stillbirth rates while moderate intervals lead to the lowest rates."

Dr. Yerushalmy's findings were based on a study of 7,151,631 births—and 211,078 stillbirths which occurred among them. His method was based on the simple assumption that in general the interval between births for women of the same age declines with increasing parity (number of births). Thus, a mother of eight at the age of 25 probably had her babies much more closely together than a mother of four at the same age. With this principle in mind, Dr. Yerushalmy compared the variation of stillbirth rates in one age group with that in other age groups.

The stillbirth rate varies greatly according to the number of children born. For mothers of *all* ages, the stillbirth rate is at a minimum of 22.2 for second births and soars upward to a rate of 115.9 for the fifteenth birth. The variation of the rate according to the age of the mother is equally distinct. It stands at the relatively high point of 33.7 for mothers from 15 to 19 years of age, drops to 23.3 for mothers from 20 to 24 years of age, and increases thereafter with the age of the mother to 56.2 in those from 40 to 44 years of age.

TABLE I. STILLBIRTH RATES (PER 1,000 TOTAL BIRTHS) BY ORDER OF BIRTH AND AGE OF MOTHER (IN FIVE-YEAR AGE GROUPS); BIRTHS TO ALL MULTIPARAS 15 TO 44 YEARS OF AGE, UNITED STATES, 1937 TO 1941

ORDER OF BIRTH	AGE OF MOTHER						
	ALL AGES	15 TO 19	20 TO 24	25 TO 29	30 TO 34	35 TO 39	40 TO 44
All multiparas	29.5	33.7	23.3	24.5	30.4	42.0	56.2
Para 2	22.2	30.1	*19.4*	19.7	24.0	35.2	51.5
Para 3	26.4	45.1	23.8	*22.6*	27.5	36.6	54.1
Para 4	30.7	74.7	30.8	*25.7*	29.8	38.9	50.8
Para 5	34.7	100.6	41.4	*29.0*	31.9	40.5	54.3
Para 6	37.0	138.4	57.0	32.7	*32.0*	40.8	52.2
Para 7	40.0		76.4	40.4	*34.1*	40.3	52.5
Para 8	44.2		110.9	52.4	*39.4*	41.1	52.5
Para 9	49.6		102.3	73.9	46.8	*45.1*	53.7
Para 10	54.4		107.7	88.3	56.9	*50.7*	53.1
Para 11	60.1		100.8	108.4	64.6	*55.5*	59.9
Para 12	67.7			140.1	90.5	64.4	*61.3*
Para 13	75.5			163.5	87.1	77.6	*68.7*
Para 14	89.1			155.8	129.2	92.6	*79.0*
Para 15	115.9			226.2	151.6	117.6	*109.4*

Figures in italics emphasize effect of the interval between births on the stillbirth rate.

The effect of the interval between births on the stillbirth rate is emphasized by the italicized figures in the various columns of Table I. These show, for example, that a mother of six at 30 years of age has a markedly lower stillbirth rate than a mother of six at 20. The repetition of this fact in all age groups emphasizes the health value of adequate spacing between pregnancies.

The lowest rates among second births are found in the mother age group of 20 to 24 years, for third, fourth, and fifth births the lowest rates are registered in the age group of 25 to 29 years. For sixth, seventh, and eighth babies the lowest stillbirth rates are registered

for mothers aged 30 to 34 years. For eighth, ninth, and tenth children the most favorable rates occur in the mother age group of 35 to 39 years. When there are twelve or more births, the best rates prevail among infants of the oldest mothers.

Not only do the minimum rates for the various parity (number of births) groups occur among groups of increasingly older mothers, but they do *not* occur among the groups of youngest mothers for any parity classification. Even among second births the best rates do not occur in mothers at the ages of from 15 to 19 years but at the ages of 20 to 24. Thus, regardless of the age of the mother or the number of children born, Dr. Yerushalmy concludes, the interval between births is a basic factor in the incidence of stillbirth. Of the total findings he says: "The results offer sufficient justification for further study with the view of determining the actual optimum intervals for the various parity and age groups. Such a study needs to be made on a very large number of births for which all the three factors, parity, age, and exact interval between births, are known."

The deaths of the following Fellows have been reported to the JOURNAL:

Dr. Edward B. Weldon, Bridgeport, Conn., on August 11.
Dr. Jules M. Brady, St. Louis, Mo., on September 8.
Dr. Herman Schwarz, New York, N. Y., on May 19.

Dr. Joseph Stokes, Jr., professor of pediatrics in the Medical School of the University of Pennsylvania, gave the first lectures of the Intermountain Pediatric Lectureship of the Medical School of the University of Utah, July 16 and 17, on "Studies of Infectious Hepatitis and Other Communicable Diseases." Dr. Ashley Weech, professor of pediatrics and head of the Children's Research Foundation of the University of Cincinnati, presented two lectures, July 26 and 27, on "The Physiologic Consequences of Inadequate Dietary Protein" and "The Role of Cortical Development in the Behavior of the Infant."

Dr. Albert D. Kaiser, professor of child hygiene at the School of Medicine of the University of Rochester, was recently awarded the Rochester Civic Medal by the Rochester Museum Association. Dr. Kaiser has also been elected for a three-year term to the Board of Trustees of the Rochester Academy of Medicine.

Two new scholars have been added to the Latin-American Scholarship List: Dr. Abel Medina H. (Nicaragua), Johns Hopkins Hospital, Baltimore, Sept. 1, 1945, and Dr. Ruben R. Buzzo (Argentina), Children's Memorial Hospital, Chicago, Ill., Sept. 4, 1945.

The Committee on Problems of the Newborn Infant of the District of Columbia Section of the American Academy of Pediatrics met May 8, 1945, to consider, at the request of the District of Columbia Health Department's Bureau of Child Hygiene, a definition of infectious (so-called epidemic diarrhea) of newborn infants.

The Committee regards the problem of defining infectious diarrhea in newborn infants as twofold: (1) The definition of symptoms that lead to suspecting that an infant may be developing infectious diarrhea for which the infant should be isolated as a suspect, and (2) the definition of symptoms that lead to a definite diagnosis of the condition.

For cases of suspected diarrhea, the Committee suggests the following definition: An infant in the neonatal period who, previously well, suddenly passes one or more very loose or liquid stools combined with sudden abnormal loss of weight (after the period of initial weight loss) or one of the other symptoms associated with this type of diarrhea such as vomiting, listlessness, drowsiness, refusal of feeding, short feeble cry, pallor, elevation of temperature, should be immediately isolated and reported to the hospital authorities as a suspect case of infectious diarrhea.

In regard to a definite diagnosis of infectious diarrhea the committee suggests that, since there is no definite way of establishing the identity of the disease, the development of similar symptoms in another exposed infant will make it essential to report both the suspect case and the new case to the health department as cases of infectious (so-called epidemic) diarrhea.

The Committee suggests that the decision be left to the health department as to whether or not a "suspect" case should be reported to them. It should be pointed out that it may prove not to be a case of infectious diarrhea.

The Committee calls attention to the importance of defining the limits for period of incubation and of isolation for cases of infectious diarrhea in infants.

ETHEL C. DUNHAM, M.D.
Chairman, Committee on Fetus and Newborn

The Pediatrician and the War

The following promotions have been reported:

Army

Lieutenant Maxwell Stillerman, Great Neck, L. I., N. Y., to Captain
Major Thomas A. Gibson, Winchester, Va., to Lieutenant Colonel
Captain R. Bruce Eldredge, Santa Monica, Calif., to Major
Captain James B. Gillespie, Urbana, Ill., to Major
Captain Noah Miller, Akron, Ohio, to Major
Captain Owen S. Ogden, Louisville, Ky., to Major
Captain Robert L. Wilder, Minneapolis, Minn., to Major

Navy

Lieutenant Commander Warren W. Quillian, Coral Gables, Fla., to Commander
Lieutenant Commander D. C. Shelby, Los Angeles, Calif., to Commander
Lieutenant Commander William R. Wilson, New Haven, Conn., to Commander

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Dr. P. F. Lucchesi, Philadelphia, Pa., has been retired from Active Service.